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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 08/819,669
Filing Date: March 17, 1997
Appellant(s): BOON et al.

Norman Hanson
For Appellant

**EXAMINER'S ANSWER**

This is in response to the Appeal Brief filed 6/1/04.

The text of those sections of Title 35 U.S. Code not included in this appeal can be found in a previous Office Action herein.

**1) Real Party of Interest.**

A statement identifying the real party of interest in contained in the Brief.

**(2) Related Appeals and Interferences Identified.**

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

**(3) Status of Claims.**

The statement of the status of claims contained in the Brief is correct.

This appeal involves claims 183-191.

Claims 1-182 have been canceled previously.

**(4) Status of Amendments After Final.**

Appellant's statement of the status of amendments contained in the Brief is correct.

**(5) Summary of Invention.**

The summary of invention contained in the Brief is correct.

Appellant's claims encompass a **MAGE family of tumor rejection antigen precursors (TRAPS)** (see page 4, line 26 – page 6 as well as page 41 of the specification).

As set forth in the Brief, the following characteristics of *MAGE TRAP proteins* are listed as follows:

*(i) they are proteins that are encoded by naturally occurring, non-mutagenized genes;*

*(ii) they are characteristic of cancer cells and are not expressed by normal cells (with the exception of testis cells);*

*(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions, and,*

*(iv) they are processed, intracellularly, into* ***tumor rejection antigens (TRAs)****, i.e. peptides, which complex to MHC molecules to form targets for cytotoxic T lymphocytes (CTLs).*

As page 6 of the Brief notes, MAGE 1-11 are encompassed by the claims and are described in the specification.

It is noted that these *MAGE TRAP protein characteristics (i) – (iv)* are consistent with the interpretation of the claimed limitations of a MAGE tumor rejection antigen precursor protein" during the prosecution of the instant application.

The examiner appreciates appellant's indication of the *MAGE TRAP protein characteristics (i) – (iv)* for clarity and convenience and will address these *characteristics* accordingly in this Examiner's Answer.

(6) **Issues.**

Appellant's statement of the issues in the Brief is correct to the extent as follows.

In order to clarify the issues, the rejections set forth herein follow appellant's four characteristics of MAGE TRAP proteins with respect to the rejections under 35 § USC 112, first paragraph, written description and enablement. In doing so, it is deemed important to set forth the facts in evidence concerning the important basic information associated with the structure and expression of the genes of the MAGE family in the Examiner's Answer for clarity and convenience. Information concerning the MAGE family disclosed in the application as-filed and in the inventor's co-authored publication **De Plaen et al.** (Immunogenetics 40: 360-369, 1994) of record is noted.

Double Patenting.

With respect to the double patenting rejection of record, the terminal disclaimer filed on 6/1/04, disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,025,474 has been reviewed and has been accepted. The terminal disclaimer has been recorded.

However, appellant has not provided a clear statement on the record that U.S. Patent No. 6,025,474 was totally commonly owned at the time the invention was made.

In agreement with appellant to expedite this application, potential double patenting issues will be addressed on the basis of a decision on the appeal in the instant application. For example, if either of the rejections under 35 USC 112, first paragraph, is maintained by limiting the genus of claimed MAGE TRAP proteins, then such a decision would affect the appropriateness of a rejection under double patenting.

(7) **Grouping of Claims.**

Appellant's Brief includes a statement that claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

Appellant has set forth a first group, drawn to claims 183, 185, 186, 188, 189 and 189.

Appellant has set forth a second group, drawn to claims 184, 187 and 190, wherein the tumor rejection antigen precursor comprises the amino acid sequence set forth in SEQ ID NO: 26, a tumor rejection antigen associated with MAGE-1.

Appellant's statement in the Brief that certain claims do not stand or fall together is not agreed with because a third group drawn to "in the form of a vaccine" recited in claims 189-191 should be included as a third Grouping of the claims. Given that a vaccine must by definition provide an immunoprotective response upon administration, claims drawn to a "form of a vaccine" should be considered separately.

The following definition of a vaccine is found on page 309 of the Illustrated Dictionary of Immunology, Cruse and Lewis, CRC Press, Boca Raton, FL, 1994.

Vaccine: Live attenuated or killed organisms or parts or products from them which contain antigens that can stimulate a specific immune response consisting of protective antibodies and T cell immunity. A vaccine should stimulate a sufficient number of memory T and B lymphocytes to yield effector T cells and antibody-producing B cells from memory cells. It should also be able to stimulate high titers of neutralizing antibodies. Invention of a vaccine into a nonimmune subject induces active immunity against the modified pathogens.

Although the examiner maintains that the rejections under 35 USC 112, first paragraph, written description and enablement should be maintained over all of the claims / Groups, it is acknowledged that the claimed limitations of Groups II and III can be considered apart from the broader generic claims of Group I.

**(8) Claims Appealed.**

The copy of the appealed claims contained in the Appendix to the Brief is correct.

**(9) Art of Record.**

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

A) Boon et al., Int. J. Cancer 54: 177-180, 1993.
B) Boon et al., Cancer Cells 1: 25-28, 1989.
C) Bork, Genome Research 10:398-400, 2000.
D) Brasseur et al., Int. J. Cancer 52: 839-841, 1992.
E) De Plaen et al., Immunogenetics 40: 360-369, 1994.
F) Ding et al., Biochem. Biophys. Commun., 202: 549–555, 1994.
G) Kirkin et al., APMIS 106: 665-679, 1998.
H) Skolnick et al., Trends in Biotech. 18:34-39, 2000.
I) Smith et al., Nature Biotechnology 15:1222-1223, 1997.
J) Stevenson, FASEB J. 5: 2250-2257, 1991.

As indicated in the previous section, a definition of a vaccine is provided herein.

(k) Illustrated Dictionary of Immunology, Cruse and Lewis, CRC Press, Boca Raton, FL, 1994. See page 309.

**(10) Grounds of Rejection.**

The following ground(s) of rejection are applicable to the appealed claims.
**Rejection Under 35 U.S.C. 112, First Paragraph, Written Description**

Claims 183-191 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention essentially for the reasons of record.

The instant claims are drawn to:

"An isolated MAGE tumor rejection antigen precursor protein, wherein said protein is encoded by a nucleic acid molecule, the complementary sequence of which hybridizes to SEQ ID NO: 8 at 0.1X SSC, 0.1% SDS, wherein said tumor rejection antigen precursor is obtainable from melanoma cells" and compositions thereof, including vaccines.

As set forth in the Brief, the following characteristics of **MAGE tumor rejection antigen precursors (TRAPs)** are listed as follows:

*(i) they are proteins that are encoded by naturally occurring, non-mutagenized genes;*

*(ii) they are characteristic of cancer cells and are not expressed by normal cells (with the exception of testis cells);*

*(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions, and,*

*(iv) they are processed, intracellularly, into* ***tumor rejection antigens (TRAs****, i.e. peptides, which complex to MHC molecules to form targets for* ***cytotoxic T lymphocytes (CTLs).***

Page 41 of the instant specification discloses that MAGE refers to a family of molecules and that the nucleic acids encoding them share a certain degree of homology and are expressed in tumor cells, including several types of tumor cells. While the family is not restricted to melanoma cells, the family is referred to as MAGE because the first members were identified in human melanoma cells. Further, it is noted that "nucleic acid molecule" refers to all species of DNA, including genomic and complementary DNA (see page 52, paragraph 2 of the instant specification). The tumor rejection antigen precursors are not expressed in most normal adult tissues but are expressed in tumor cells (see page 6, paragraph 1 of the specification).

Tumor rejection antigen precursors (TRAPs) are processed to form the presentation of tumor rejection antigens (TRAs) (page 2 of the specification), including but not limited to those most characteristic of a particular tumor (page 4 of the specification)

The specification does not identify the key structural elements that identify the nucleic acids that encode a tumor rejection antigen precursor, broadly encompassed by the claimed invention. While the specification discloses a single nucleic acid sequence species for each of MAGE 1-11, there is insufficient information concerning identifying the key structural and functional characteristics of nucleic acids which complementary nucleic acids hybridize to SEQ ID NO: 8 under certain conditions and encode a tumor rejection antigen precursor protein, in particular, a MAGE tumor rejection antigen precursor protein as it reads on *MAGE TRAP characteristics (i) – (iv)* .

While it is noted that SEQ ID NO: 8 hybridizes with the nucleic acid of each disclosed MAGE species (e.g. MAGE-1, MAGE-2, MAGE-3, etc.), not all nucleic acids that hybridize with SEQ ID NO: 8 are necessarily MAGE tumor rejection antigen precursors that satisfy the *four elements of TRAPS listed above*.

With respect to *(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions*, the claims do not recite all of the stringent conditions set forth on pages 49-50 in Example 32, as asserted and relied upon by appellant.

The present **specification** disclosed the following information.

(a) The gene for MAGE-1 extends over 4.5 kb as shown in Figure 8 (see Example 21 on page 40 of the instant **specification**).

(b) MAGE refers to a family of molecules, which share a certain degree of homology and which are expressed in tumor cells (see Example 23 on page 41 of the instant **specification**).

(c) In order to determine if smaller segments of the 2.4 kb fragment could transfer the expression of antigen E, smaller pieces corresponding to the larger gene were prepared (see Example 22 on page 40 of the instant **specification**).

(d) The probing of cDNA revealed two closely related cDNAs which when tested, did not transfer expression of antigen E, but did show substantial homology to the first cDNA segments (see Example 23 on page 41 of the instant **specification**).

(e) The DNA probes corresponding to MAGE –1, MAGE –2 and MAGE-3 cross-hybridized to a considerable extent, providing an inability to distinguish among said MAGEs. (see Example 25 on page 43 of the **specification**).

(f) In testing a panel of melanoma cell lines for the expression of MAGE-1, -2 and –3, the specification discloses that it is impossible to exclude formally that some positive PCR results do not reflect the expression of one of the three characterized MAGE genes but that of yet another closely related gene that would share the sequence of the priming and hybridizing oligonucleotides (see page 44, lines 20-25 of the **specification**).

(g) Cells transfected expressing antigen E were able to stimulate anti-E cytotoxic T lymphocyte 82/30 to release tumor necrosis factor (TNF), as a measure of CTL stimulation. One transfectant presented antigens out of 70,000 genetic resistant transfectants (see page 35, paragraph 2 in Example 18 of the **specification**).

(h) Given that exon 3 of MAGE-1 was shown to transfer the expression of antigen E, only one synthetic peptide set forth in SEQ ID NO: 26 derived from exon 3 was shown to confer sensitivity to the anti-E cytotoxic T lymphocytes (see Example 34 on pages 50-51 of the **specification**).

(i) In order to identify a transfectant expressing antigen F, a yield of two positives out of 17,500 transfectants, resulted from 14 groups of about 50,000 cosmids were analyzed (see Examples 28-29 on pages 47-48 of the **specification**).

(j) Example 30 identifies MAGE-4 from a sample of human sarcoma cell line, which hybridized to the 2.4 kb fragments (see Example 30 on page 48 of the **specification**).

(k) On the basis of homology to MAGE 1-4, MAGE 5 was identified, and corresponds to SEQ ID NO: 16 (see Example 31 on pages 48-49 of the **specification**).

(l) Oligos derived from SEQ ID NO: 8 were used to identify a sequence differing from previously identified MAGE 1-5, wherein said sequence was named MAGE-6 (see Example 32 on pages 49-50 of the **specification**).

(m) In addition, experiments with cosmid library from PHA-activated lymphocytes of MZ2 with the 2.4 MAGE 1 fragment as a probe yielded MAGE 7 (see Example 33 on page 50 of the **specification**).

(n) Additional screening yielded MAGE 8-11 (see Example 33 on page 50 of the **specification**).

**In addition to the specification, De Plaen et al.** (Immunogenetics 40: 360-369, 1994; of record) disclosed the following information as a review of the MAGE family.

To clarify some important basic information concerning the structure and expression of the genes of the MAGE family, the following information disclosed in the inventor's co-authored publication **De Plaen et al**. (Immunogenetics 40: 360-369, 1994) of record is noted herein.

(a) The human gene MAGE-1 directs expression of a tumor antigen recognized on a melanoma by autologous cytolytic T lymphocytes (CTLs) (see entire document, particularly the Abstract and Discussion of **De Plaen et al**.).

(b) Probing cosmid libraries with a MAGE-1 nucleic acid sequence, 11 closely related genes have been identified (see entire document, particularly the Abstract and Discussion of **De Plaen et al.**).

(c) These 11 MAGE genes have their entire coding sequence located in the last exon, which shows 64-85% nucleic acid identity with that of MAGE-1 (see entire document, particularly the Abstract and Discussion of **De Plaen et al.**).

(d) Six genes of the MAGE family (MAGE-1, -2, -3, -4, -6 and -12; have been found to be expressed in a number of tumors of various histological types (see Abstract and Expression of MAGE genes on pages 366-367 of **De Plaen et al.**).

Note that the MAGE-12 discussed in **De Plaen et al.** is not disclosed in the specification as-filed. When **De Plaen et al.** describes 11 MAGE genes, this does not include MAGE-7. See (j) herein.

(e) MAGE-5, -8, -9, -10 and -11 genes were very weakly expressed in all samples that have been examined (see page 367, column 1, paragraph 2 **De Plaen et al.**).

(f) None of the MAGE genes were expressed in a large panel of healthy tissues, with the exception of testis and placenta (see Abstract and Expression of MAGE genes on pages 366-367 of **De Plaen et al.**).

(g) The structure of genes MAGE-5 and 7-11 have not been completely defined because no cDNA clones have obtained at least up to the 1994 publication date of **De Plaen et al.** (see page 364, column 2, first full paragraph of **De Plaen et al.**).

(h) The sequences of the MAGE genes do not show significant homology with known sequences in the databases (see page 365, column 1, lines 2-4 below Figure 4 of **De Plaen et al.**).

(i) Most of the putative MAGE proteins are 309-319 amino acids long. MAGE-2-6 and 8-12 proteins have 57% - 77% amino acid sequence identity with MAGE-1 (see page 365, column 1, paragraph 1 of **De Plaen et al**).

(j) In this **De Plaen et al.** publication, MAGE-7 was not included for comparison, because it was not found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes (see page 365, column 1, paragraph 1 of **De Plaen et al**).

(k) Several lines of evidence suggest that MAGE genes show little variation or polymorphism from one individual to another (see page 365, column 2, paragraph 1 of **De Plaen et al.**).

(l) Given the conservation of sequences in MAGE genes, it has been suggested that the proteins produced by all of these genes may exert very similar functions. At the time the invention was made and post-filing, there was no indication regarding this function (see page 367, column 2, paragraph 3 of **De Plaen et al**.).

(m) It is likely that various regions of the different MAGE proteins can contribute peptides combining with various HLA class I molecules (page 368, column 1, paragraph 2 of **De Plaen et al.)**.

In contrast to appellant's assertions, the instant specification does not provide for 11 species that meet the key characteristics of MAGE, including:

*(i) they are proteins that are encoded by naturally occurring, non-mutagenized gene;*

*(ii) they are characteristic of cancer cells and are not expressed by normal cells (with the exception of testes cells;*

*(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions; and*

*(iv) they are processed, intracellularly, into TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs.*

The specification does not provide for the cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein itself for each of the 11 species of MAGE 1-11 in the specification as filed.

The instant specification does not appear to provide for the expression of MAGE 5-11 on normal and cancer cells.

The instant specification does not appear to provide for the ability of MAGE 4-11 transfectants to stimulate cytotoxic T lymphocytes, nor provide for the cytotoxic T lymphocytes (CTLs) to test the properties of MAGE 4-11 as TRAPs.

Further, the specification as filed does not provide for the tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs), other than the specific peptide SEQ ID NO: 26 which forms a complex with HLA-A1 and stimulates proliferation of CTLs and which is specific for MAGE-1.

As acknowledged on page 52, paragraph 1 of the instant specification, the instant disclosure, including the examples, provides to the skilled artisan a methodology for isolating nucleic acid molecules which code for tumor rejection antigen precursors.

As disclosed on page 55, paragraph 1 of the instant specification, the sequences code for "tumor rejection antigen precursors" (TRAPS) which, in turn, are processed into tumor rejection antigens (TRAs). Isolated forms of both of these categories are described herein, including specific examples of each. Perhaps their most noteworthy aspect is as vaccines for treating various cancerous conditions. The evidence points to presentation of TRAs on tumor cells, followed by the development of an immune response and deletion of the cells. The examples show that when various TRAs are administered to cells, a CTL response is mounted and presenting cells are deleted. This is behavior characteristic of vaccines, and hence TRAPS, which are processed into TRAs, and the TRAs themselves may be used either alone or in pharmaceutically appropriate compositions, as vaccines.

As disclosed on page 30, paragraph 2 of the instant specification, in isolating the pertinent nucleic acid sequence for a tumor rejection antigen precursor, the techniques developed by appellant showed that a recipient cell is needed which fulfills two criteria: (i) the recipient cell must not express the TRAP of interest under normal conditions, and (ii) it must express the relevant class I HLA molecule.

Therefore, it was necessary to have the appropriate CTLs readily available and know what was the relevant class I HLA molecule associated with each MAGE TRAP protein in order to determine whether a MAGE TRAP protein satisfied the four criteria *(i) – (iv)* for a MAGE TRAP.

Nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8 do not provide a sufficient written description provision of 35 USC 112, first paragraph for a genus of diverse tumor rejection antigen precursors, particularly the four characteristics *(i) – (iv)* for MAGE TRAP proteins.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 to any or all of the TRAP properties *(i) – (iv)* outlined above.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 to MAGE TRAP protein expression itself or expression of a MAGE TRAP protein on a cancer cell.

For example, the disclosed MAGE-7 has not been found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes (see page 365, column 1, paragraph 1 of **De Plaen et al**).

Again, as indicated above, the specification as-filed does not provide for the cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein itself for each of the 11 species of MAGE 1-11 in the specification as-filed.

Also, there is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 and the tumor rejection antigens (TRAs) or peptides which complex to MHC molecules to form targets for CTLs.

There is insufficient correlation of the structure of SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 to the immunogenicity of MAGE TRAP proteins or to the TRAs that are complexed to MHC molecules to form targets for CTLs.

Again, as indicated above, the specification as filed does not provide for the tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs), other than the specific peptide SEQ ID NO: 26 which forms a complex with HLA-A1 and stimulates proliferation of CTLs and which is specific for MAGE-1.

Importantly, it is noted that claims are not even limited to SEQ ID NO: 8 itself, but rather the claims recite "nucleic acid molecules that hybridize to SEQ ID NO: 8", thereby a greater diversity of nucleic acid sequences and, in turn, a greater diversity of amino acid sequences encoding a MAGE TRAP protein are encompassed by the claims.

As noted above with respect to *(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions*, the claims do not recite all of the stringent conditions set forth on pages 49-50 in Example 32, as asserted and relied upon by appellant.

While appellant relies upon hybridizing nucleic acids to SEQ ID NO: 8 as the key common structural feature, the specification does not account for the distinguishing structural, expression and functional characteristics of each of the 11 MAGE TRAP species disclosed in the specification as-filed, not all of which meet the four characteristics (*(i)-(iv)*) of MAGE TRAPs asserted in the Brief.

While appellant relies upon hybridizing nucleic acids as the key common structural feature, appellant does not account for the absence of the instant disclosure to provide for a known or disclosed correlation between the function of a MAGE TRAP protein with a particular structure (see *TRAP characteristics (i), (ii), (iii), (iv)*), including a genus of MAGE tumor rejection antigen precursor proteins encoded by nucleic acids the complement of which hybridizes to SEQ ID NO: 8 under the written description provision of 35 USC 112, first paragraph.

The description of appellant's instant disclosure as well as appellant's co-authored reference **De Plaen et al**. are not consistent with appellant's assertions in the Brief that appellant has provided 11 species that meet the claimed limitations, namely a MAGE TRAP protein that possesses the *MAGE TRAP characteristics (i), (ii), (iii), (iv)* as addressed herein. The MAGE TRAPS disclosed in the application as filed differ from one another on both structural and functional attributes to such an extent that the possession of one does not render possession of another MAGE TRAP protein that possesses the *MAGE TRAP characteristics (i), (ii), (iii), (iv)* as addressed herein.

Written description requires for the functional characteristics *(see TRAP characteristics (i) – (iv))* of a MAGE TRAP protein to be coupled with a disclosed correlation to a structure (i.e. nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8). Sufficient disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described rather than merely describing the claimed subject matter in functional terms as a MAGE TRAP protein which are encoded by nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8.

As indicated above based upon the instant disclosure as filed as well as by the co-inventors own work in De Plaen et al., the 11 species disclosed in the specification as filed do not satisfy the four characteristics of MAGE TRAP proteins.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed tumor antigen precursor and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences.

The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

With respect to characteristic *(iv) they are processed, intracellularly, into TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs* and the recitation of "vaccine" in claim 189-191, the following is noted.

As described on page 55, paragraph 1 of the specification, the disclosure make clear that the sequences code for **tumor rejection antigen precursors (TRAPS** which, in turn are processed into **tumor rejection antigens (TRAs)**. The evidence points to presentation of TRAs on tumor cells, followed by the development of an immune response and deletion of the cells. TRAPS which are processed into TRAs and the TRAs themselves may be used either alone or in pharmaceutically appropriate compositions as vaccines.

The following definition of a vaccine is found on page 309 of the Illustrated Dictionary of Immunology, Cruse and Lewis, CRC Press, Boca Raton, FL, 1994.

Vaccine: Live attenuated or killed organisms or parts or products from them which contain antigens that can stimulate a specific immune response consisting of protective antibodies and T cell immunity. A vaccine should stimulate a sufficient number of memory T and B lymphocytes to yield effector T cells and antibody-producing B cells from memory cells. It should also be able to stimulate high titers of neutralizing antibodies. Invention of a vaccine into a nonimmune subject induces active immunity against the modified pathogens.

Even the known MAGE molecules exhibit extremely low immunogenicity and initiation of a strong immune response to tumor antigens is vivo is an extremely rare event (see page 674, paragraph 2 of Kirkin et al., APMIS 106: 665-679, 1998).

In discussing the structure and expression of MAGE family genes, De Plaen et al. (Immunogenetics 40: 360-369, 1994) note: "Throughout the MAGE family ..., there is considerable conservation of hydrophilic and hydrophobic regions, suggesting that the proteins produced by all these genes may exert very similar function. At the present time, however, there is no indication regarding this function." (see page 367, column 2, paragraph 2).

It is noted that the MAGE genes do not seem to be expressed in normal tissues except testis and placenta (see De Plaen et al., page 368, column 1, paragraph 2). While the MAGE genes may have the potential to code for antigens that could be targets for specific anti-tumor T lymphocyte responses, such responses would rely upon various regions of the different MAGE proteins contributing peptides that combine with various HLA class I molecules (page 368, column 1, paragraph 2).

The reliance upon the function of the claimed tumor rejection antigen precursors depends, in part, upon the antigen processing and presentation of MAGE-derived peptides, which, in turn, can form targets for cytotoxic T cells directed against these peptides.

While such efforts may provide the groundwork for determining a MAGE tumor antigen precursor, "it is difficult to predict whether therapeutic success will be achieve, even if a significant increase in anti-tumor cytotoxic lymphocytes is obtained by immunization" (see Boon et al. (Int. J. Cancer 54: 177-180, 1993; see page 178, column 2, paragraph 2).

Further, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

Although appellant has argued and distinguished between different classes of tumor or tumor-associated antigens (e.g. tum- and TSTA) in defining the MAGE family encompassed by the claimed invention, the following of record was provided to show that defining human tumor antigens, including human tumor antigens that result to stimulating cytotoxic T lymphocytes to tumors was difficult at the time the invention was made.

Defining human tumor antigens or tumor antigen precursors has not been readily apparent to the skilled artisan. For example, Stevenson (FASEB J 5: 2250-2257, 1991) reviews tumor vaccines and tumor antigens (see entire document) and notes the following. "The first problem in discussing tumor antigens is one of nomenclature. The original definition of a tumor-specific transplantation antigen (TSTA) was an operational one based on the ability of a sensitizing dose of a particular tumor given to syngeneic animals to elicit T cell-mediated rejection of a subsequent challenge of those tumor cells" (see page 2251, column 1, paragraph 1 of Tumor Antigens). "Attempts to delineate

tumor antigens in human tumors apart from the virally encoded antigens have been fraught with difficulty" (page 2251, column 2, paragraph 2).

Boon et al. (Cancer Cells 1: 25-28, 1989) discloses that "On the basis of these results, we now have a plausible explanation for the stability, frequency, and diversity of tum- variants. They are stable because they arise as a result of point mutations. They are extremely frequent and diverse, because mutations occurring throughout the whole genome can lead to the production of new antigenic peptides binding to class I MHC molecules so as to be recognized by the T lymphocytes of the host. They do not stimulate the production of antibodies because B cells may not be adapted to the recognition of a very low density of antigenic peptides bound to class I molecules" (see page 26, column 2, paragraph 2). "Are the TSTA like tum- antigens, the result of mutations occurring throughout the genome? Certainly, the large diversity of TSTA would be consistent with this notion" (see page 26, column 2, paragraph 3). "It would also imply that the TSTA bear no functional relation with the cellular modifications that lead to malignant transformation" (see page 27, column 1). "Only the cloning of the relevant genes and comparison of their sequences with those found in normal cells can give a complete answer to the problem. Thus, for man, the genetic approach probably will be required not only to establish the nature of TSTA but also to demonstrate their existence" (page 28, column 1).

Therefore, the skilled artisan recognized the difficulty in defining a human tumor antigen, regardless of the type of tumor antigen (e.g tum- antigens, TSTA, MAGE), whether it was at the time the invention was made and recognized the requirement to demonstrate its existence by possession.

Here, the specification does not provide sufficient written description of a genus of MAGE tumor rejection antigen precursors based upon the limited disclosure/recitation of a one nucleic acid encoding MAGE-1 or upon the limited information (nucleic acids but not cDNA sequences nor amino acid sequences nor isolation of MAGE TRAP protein) on each one of MAGE 1-11 TRAP proteins that can be isolated from melanoma cells. There is insufficient written description of the structure / sequences of nucleic acids or which the complementary sequence can hybridize to SEQ ID NO: 8 and encode a genus of diverse tumor rejection antigen precursors and, in turn, provide the appropriate structural and functional attributes of a genus of tumor antigen precursors, with distinct structural, expression and functional properties.

Further, given the inability of each species of the disclosed MAGE 1-11 to satisfy the four criteria of TRAPs (see above *TRAP characteristics (i) – (iv)*) as well as the diversity of structure of the members of the MAGE family (e.g. MAGE-2-6 and 8-12 have 57% - 77% amino acid identity with MAGE-1; see page 365, column 1, paragraph 1 of **De Plaen et al.**); there is insufficient written description of a genus of MAGE tumor rejection antigen precursor proteins encoded by nucleic acids the complement of which hybridizes to SEQ ID NO: 8 under the written description provision of 35 USC 112, first paragraph.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

The instant disclosure does not provide for the possession of the functional characteristics of a MAGE TRAP coupled with a known or disclosed correlation between the function of a MAGE TRAP with a particular structure (see *TRAP characteristics (i), (ii), (iii), (iv)*), including a genus of MAGE tumor rejection antigen precursor proteins encoded by nucleic acids the complement of which hybridizes to SEQ ID NO: 8 under the written description provision of 35 USC 112, first paragraph.

Appellant has been directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

**Rejection Under 35 U.S.C. 112, First Paragraph, Enablement**

Claims 183-191 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a MAGE-1 tumor antigen precursor encoded by SEQ ID NO: 8; does not reasonably provide enablement for any "an isolated MAGE tumor rejection antigen precursor protein, wherein said protein is encoded by a nucleic acid molecule, the complementary sequence of which hybridizes to SEQ ID NO: 8 at 0.1X SSC, 0.1% SDS, wherein said tumor rejection antigen precursor is obtainable from melanoma cells".

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to:

"An isolated MAGE tumor rejection antigen precursor protein, wherein said protein is encoded by a nucleic acid molecule, the complementary sequence of which hybridizes to SEQ ID NO: 8 at 0.1X SSC, 0.1% SDS, wherein said tumor rejection antigen precursor is obtainable from melanoma cells" and compositions thereof, including vaccines.

As set forth in the Brief, the following characteristics of **MAGE tumor rejection antigen precursors (TRAPs)** are listed as follows:

*(i) they are proteins that are encoded by naturally occurring, non-mutagenized genes;*

*(ii) they are characteristic of cancer cells and are not expressed by normal cells (with the exception of testes cells);*

*(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions, and,*

*(iv) they are processed, intracellularly, into* ***tumor rejection antigens (TRAs****, i.e. peptides, which complex to MHC molecules to form targets for* ***cytotoxic T lymphocytes (CTLs).***

Appellant has not provided sufficient biochemical information (e.g. amino acid sequences) that distinctly identifies the breadth of MAGE tumor rejection antigen precursor proteins encoded by nucleic acids encoding tumor rejection antigen precursor proteins and which hybridize to SEQ ID NO: 8, encompassed by the claimed invention.

As indicated previously, appellant was invited to limit the claims either to SEQ ID NO: 7 / SEQ ID NO: 8 that read on MAGE-1 as the elected invention (see appellant's election filed 12/9/97).

While the recitation of "an isolated MAGE tumor rejection antigen precursor protein" may have some notion of the properties of the claimed molecule(s), claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make and use the "MAGE tumor rejection antigen precursor proteins", commensurate in scope with the claimed invention.

There is insufficient guidance and direction as to how to make and use the breadth of MAGE tumor rejection antigen precursor proteins encoded by nucleic acids that hybridize to SEQ ID NO: 8; other than MAGE-1 encoded by SEQ D NO: 8 in the absence of structural, expression or functional attributes that define a MAGE tumor rejection antigen precursor proteins that satisfy *TRAP characteristics (i) - (iv)*.

Tumor antigen precursors are processed to form the presentation of tumor rejection antigens (page 6 of the specification), including but not limited to those most characteristic of a particular tumor (page 8 of the specification)

A person of skill in the art was not enabled to make and use the breadth of MAGE tumor rejection antigen precursors, which can be processed to form the presentation of tumor rejection antigens and be characteristic of a particular tumor, commensurate in scope with the claimed invention. The skilled artisan would not have predicted that all that is required for a MAGE tumor rejection antigen precursor protein with *characteristic properties (i) – (iv)* is that it can be encoded by a nucleic acid of which hybridizes to SEQ ID NO: 8. A skilled artisan would have expected that critical structural, expression and functional attributes needed to be tested empirically rather than relying upon hybridizing nucleic acids to SEQ ID NO: 8 alone to provide for a nucleic acid to encode a MAGE tumor rejection antigen precursor protein and its ability to be processed to form a tumor rejection antigen characteristic of a particular tumor.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases.

For example, Skolnick et al. (Trends in Biotech. 18:34-39, 2000) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36).

Similarly, Bork (Genome Research 10:398-400, 2000) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399).

Smith et al. (Nature Biotechnology 15:1222-1223, 1997) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene

With respect to the claimed MAGE TRAP proteins, page 41 of the instant specification discloses that MAGE refers to a family of molecules and that the nucleic acids encoding them share a certain degree of homology and are expressed in tumor cells, including several types of tumor cells. While the family is not restricted to melanoma cells, the family is referred to as MAGE because the first members were identified in human melanoma cells. Further, it is noted that "nucleic acid molecule" refers to all species of DNA, including genomic and complementary DNA (see page 52, paragraph 2 of the instant specification). The tumor rejection antigen precursors are not expressed in most normal adult tissues but are expressed in tumor cells (see page 6, paragraph 1 of the specification).

Tumor rejection antigen precursors (TRAPs) are processed to form the presentation of tumor rejection antigens (TRAs) (page 2 of the specification), including but not limited to those most characteristic of a particular tumor (page 4 of the specification).

The specification does not identify the key structural elements that identify the nucleic acids that encode a tumor rejection precursor antigen, broadly encompassed by the claimed invention. While the specification discloses a single nucleic acid species for each of MAGE 1-11, there is insufficient information concerning identifying the key structural and functional characteristics of nucleic acids which complementary nucleic acids hybridize to SEQ ID NO: 8 under certain conditions and encode a tumor rejection antigen precursor protein, in particular, a MAGE tumor rejection antigen precursor protein.

While it is noted that SEQ ID NO: 8 hybridizes with the nucleic acid of each disclosed MAGE species (e.g. MAGE-1, MAGE-2, MAGE-3, etc.), not all nucleic acids that hybridize with SEQ ID NO: 8 are necessarily MAGE tumor rejection antigen precursors that satisfy the *four characteristics (i) – (iv)* of MAGE TRAPs.

With respect to *(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions*, the claims do not recite the stringent conditions set forth on pages 49-50 in Example 32, as asserted and relied upon by appellant.

**The following evidence presented herein is reiterated from above in the rejection under written description but is set forth in smaller print to save space. The examiner apologizes for any inconvenience to appellant and to the Board of Appeals in this manner**.

The present **specification** disclosed the following information.

(a) The gene for MAGE-1 extends over 4.5 kb as shown in Figure 8 (see Example 21 on page 40 of the instant **specification**).

(b) MAGE refers to a family of molecules, which share a certain degree of homology and which are expressed in tumor cells (see Example 23 on page 41). .

(c) In order to determine if smaller segments of the 2.4 kb fragment could transfer the expression of antigen E, smaller pieces corresponding to the larger gene were prepared (see Example 22 on page 40).

(d) The probing of cDNA revealed two closely related cDNAs which when tested, did not transfer expression of antigen E, but did show substantial homology to the first cDNA segments (see Example 23 on page 41).

(e) The DNA probes corresponding to MAGE –1, MAGE –2 and MAGE-3 cross-hybridized to a considerable extent, providing an inability to distinguish among said MAGEs. (see Example 25 on page 43 of the **specification**).

(f) In testing a panel of melanoma cell lines for the expression of MAGE-1, -2 and –3, the specification discloses that it is impossible to exclude formally that some positive PCR results do not reflect the expression of one of the three characterized MAGE genes but that of yet another closely related gene that would share the sequence of the priming and hybridizing oligonucleotides (see page 44, lines 20-25 of the **specification**).

(g) Cells transfected expressing antigen E were able to stimulate anti-E cytotoxic T lymphocyte 82/30 to release tumor necrosis factor (TNF), as a measure of CTL stimulation. One transfectant presented antigens out of 70,000 genetic resistant transfectants (see page 35, paragraph 2 in Example 18 of the **specification**).

(h) Given that exon 3 of MAGE-1 was shown to transfer the expression of antigen E, only one synthetic peptide set forth in SEQ ID NO: 26 derived from exon 3 was shown to confer sensitivity to the anti-E cytotoxic T lymphocyte (see Example 34 on pages 50-51 of the **specification**).

(i) In order to identify a transfectant expressing antigen F, a yield of two positives out of 17,500 transfectants, resulted from 14 groups of about 50,00 cosmids were analyzed (see Examples 28-29 on pages 47-48 of the **specification**).

(j) Example 30 identifies MAGE-4 from a sample of human sarcoma cell line, which hybridized to the 2.4 kb fragments (see Example 30 on page 48 of the **specification**).

(k) On the basis of homology to MAGE 1-4, MAGE 5 was identified, and corresponds to SEQ ID NO: 16 (see Example 31 on pages 48-49 of the **specification**).

(l) Oligos derived from SEQ ID NO: 8 were used to identify a sequence differing from previously identified MAGE 1-5, wherein said sequence was named MAGE-6 (see Example 32 on pages 49-50 of the **specification**).

(m) In addition, experiments with cosmid library from PHA-activated lymphocytes of MZ2 with the 2.4 MAGE 1 fragment as a probe yielded MAGE 7 (see Example 33 on page 50 of the **specification**).

(n) Additional screening yielded MAGE 8-11 (see Example 33 on page 50 of the **specification**).

**In addition to the specification, De Plaen et al.** (Immunogenetics 40: 360-369, 1994; of record) disclosed the following information as a review of the MAGE family.

To clarify some important basic information concerning the structure and expression of the genes of the MAGE family, the following information disclosed in the inventor's co-authored publication **De Plaen et al**. (Immunogenetics 40: 360-369, 1994) of record is noted.

(a) The human gene MAGE-1 directs expression of a tumor antigen recognized on a melanoma by autologous cytolytic T lymphocytes (CTLs) (see entire document, particularly the Abstract and Discussion of **De Plaen et al.**).

(b) Probing cosmid libraries with a MAGE-1 sequence, 11 closely related genes have been identified (see entire document, particularly the Abstract and Discussion of **De Plaen et al.**).

(c) These 11 MAGE genes have their entire coding sequence located in the last exon, which shows 64-85% identity with that of MAGE-1 (see entire document, particularly the Abstract and Discussion of **De Plaen et al.**).

(d) Six genes of the MAGE family (MAGE 1, 2, 3, 4, 6 and 12; Note MAGE-12 is not disclosed in the specification as filed) have been found to be expressed in a number of tumors of various histological types (see Abstract and Expression of MAGE genes on pages 366-367 of **De Plaen et al.**).

(e) MAGE 5, 8, 9, 10 and 11 were very weakly expressed in all samples that have been examined page 367, column 1, paragraph 2 **De Plaen et al.**).

(f) None were expressed in a large panel of healthy tissues, with the exception of testis and placenta (see Abstract and Expression of MAGE genes on pages 366-367 of **De Plaen et al.**).

(g) The structure of genes MAGE-5 and 7-11 have not been completely defined because no cDNA clones have obtained up to now (see page 364, column 2, first full paragraph of **De Plaen et al.**).

(h) The sequences of the MAGE genes do not show significant homology with known sequences in the databases (see page 365, column 1, lines 2-4 below Figure 4 of **De Plaen et al.**).

(i) Most of the putative MAGE proteins are 309-319 amino acids long. MAGE proteins 2-6 and 8-12 have 57% - 77% identity with MAGE-1 (see page 365, column 1, paragraph 1 of **De Plaen et al**).

(j) In this publication, MAGE-7 was not included for comparison, because it was not found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes (see page 365, column 1, paragraph 1 of **De Plaen et al**).

(k) Several lines of evidence suggest that MAGE genes show little variation or polymorphism from one individual to another (see page 365, column 2, paragraph 1 of **De Plaen et al.**).

(l) Given the conservation of sequences in MAGE genes, it has been suggested that the proteins produced by all of these genes may exert very similar functions. At the time the invention was made and post-filing, there was no indication regarding this function (see page 367, column 2, paragraph 3 of **De Plaen et al.**).

(m) It is likely that various regions of the different MAGE proteins can contribute peptides combining with various HLA class I molecules (page 368, column 1, paragraph 2 of **De Plaen et al.**

In contrast to appellant's assertions, the specification does not provide for 11 species that meet the key characteristics of MAGE, including:

*(i) they are proteins that are encoded by naturally occurring, non-mutagenized gene;*

*(ii) they are characteristic of cancer cells and are not expressed by normal cells (with the exception of testes cells;*

*(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions; and*

*(iv) they are processed, intracellularly, into TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs.*

The specification does not provide for the cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein for each of the 11 species of MAGE 1-11 in the specification as filed.

The instant specification does not appear to provide for the expression of MAGE 5-11 on normal and cancer cells.

The instant specification does not appear to provide for the ability of MAGE 4-11 transfectants to stimulate cytotoxic T lymphocytes, nor provide for the cytotoxic T lymphocytes (CTLs) to test the properties of MAGE 4-11 as TRAPs.

Further, the specification as filed does not provide for the tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs), other than the specific peptide SEQ ID NO: 26 which forms a complex with HLA-A1 and stimulates proliferation of CTLs and which is specific for MAGE-1.

As acknowledged on page 52, paragraph 1 of the instant specification, the instant disclosure, including the examples, provides to the skilled artisan a methodology for isolating nucleic acid molecules which code for tumor rejection antigen precursors.

Such nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8 do not provide a sufficient enabling disclosure under 35 USC 112, first paragraph, for a genus of diverse tumor rejection antigen precursors, particularly the four characteristics for MAGE TRAP proteins, acknowledged by appellant.

The instant specification provides for methods for screening and evaluating nucleic acids that hybridize to SEQ ID NO: 8 to determine if they are a member of the MAGE TRAP protein family. The disclosed methodology provides for a plan or a starting point for those of skill in the art to experiment practicing the claimed invention. The instant application does not provide the necessary link between nucleic acids that hybridize to SEQ ID NO: 8, various assays to determine the relatedness of such hybridizing nucleic acids to one another, the cellular expression of MAGE 1-3 and the isolation of just one tumor rejection antigen (TRA) (i.e. SEQ ID NO: 26) from just one MAGE TRAP (i.e. MAGE-1) to enable a skilled artisan to make and use a family of MAGE TRAP proteins that satisfy the four characteristics of *(i)-(iv)* defining MAGE TRAPS, as asserted and claimed by appellant.

As indicated above based upon the instant disclosure as filed as well as by the co-inventors own work in **De Plaen et al.**, the 11 species disclosed in the specification as filed do not satisfy the four characteristics of MAGE TRAPs.

With respect to characteristic *(iv) they are processed, intracellularly, into TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs* and the recitation of "vaccine" in claims 189-191, the following is noted.

As described on page 55, paragraph 1 of the specification, the disclosure make clear that the sequences code for **tumor rejection antigen precursors (TRAPS** which, in turn are processed into **tumor rejection antigens (TRAs)**. The evidence points to presentation of TRAs on tumor cells, followed by the development of an immune response and deletion of the cells. TRAPS which are processed into TRAs and the TRAs themselves may be used either alone or in pharmaceutically appropriate compositions as vaccines.

The following definition of a vaccine is found on page 309 of the Illustrated Dictionary of Immunology, Cruse and Lewis, CRC Press, Boca Raton, FL, 1994.

Vaccine: Live attenuated or killed organisms or parts or products from them which contain antigens that can stimulate a specific immune response consisting of protective antibodies and T cell immunity. A vaccine should stimulate a sufficient number of memory T and B lymphocytes to yield effector T cells and antibody-producing B cells from memory cells. It should also be able to stimulate high titers of neutralizing antibodies. Invention of a vaccine into a nonimmune subject induces active immunity against the modified pathogens.

Even the known MAGE molecules exhibit extremely low immunogenicity and initiation of a strong immune response to tumor antigens is vivo is an extremely rare event (see page 674, paragraph 2 of Kirkin et al., APMIS 106: 665-679, 1998).

In discussing the structure and expression of MAGE family genes, **De Plaen et al**. (Immunogenetics 40: 360-369, 1994) note: "Throughout the MAGE family ..., there is considerable conservation of hydrophilic and hydrophobic regions, suggesting that the proteins produced by all these genes may exert very similar function. At the present time, however, there is no indication regarding this function." (see page 367, column 2, paragraph 2).

It is noted that the MAGE genes do not seem to be expressed in normal tissues except testis and placenta (see **De Plaen et al**., page 368, column 1, paragraph 2). While the MAGE genes may have the potential to code for antigens that could be targets for specific anti-tumor T lymphocyte responses, such responses would rely upon various regions of the different MAGE proteins contributing peptides that combine with various HLA class I molecules (page 368, column 1, paragraph 2).

Therefore, the reliance upon the function of the claimed tumor rejection antigen precursor proteins depends, in part, upon the antigen processing and presentation of MAGE-derived peptides, which, in turn, can form targets for cytotoxic T cells directed against these peptides.

While such efforts may provide the groundwork for determining a MAGE tumor antigen precursor, "it is difficult to predict whether therapeutic success will be achieve, even if a significant increase in anti-tumor cytotoxic lymphocytes is obtained by immunization" (see Boon et al. (Int. J. Cancer 54: 177-180, 1993; see page 178, column 2, paragraph 2).

Further, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should

nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

Although appellant has argued and distinguished between different classes of tumor or tumor-associated antigens (tum- or TSTA) in defining the MAGE family encompassed by the claimed invention, the following of record was provided to show that defining human tumor antigens, including human tumor antigens that result to stimulating cytotoxic T lymphocytes to tumors was difficult at the time the invention was made.

Defining human tumor antigens or tumor antigen precursors has not been readily apparent to the skilled artisan. For example, Stevenson (FASEB J 5: 2250-2257, 1991) reviews tumor vaccines and tumor antigens (see entire document) and notes the following. "The first problem in discussing tumor antigens is one of nomenclature. The original definition of a tumor-specific transplantation antigen (TSTA) was an operational one based on the ability of a sensitizing dose of a particular tumor given to syngeneic animals to elicit T cell-mediated rejection of a subsequent challenge of those tumor cells" (see page 2251, column 1, paragraph 1 of Tumor Antigens). "Attempts to delineate tumor antigens in human tumors apart from the virally encoded antigens have been fraught with difficulty" (page 2251, column 2, paragraph 2).

Boon et al. (Cancer Cells 1: 25-28, 1989) discloses that "On the basis of these results, we now have a plausible explanation for the stability, frequency, and diversity of tum- variants. They are stable because they arise as a result of point mutations. They are extremely frequent and diverse, because mutations occurring throughout the whole genome can lead to the production of new antigenic peptides binding to class I MHC molecules so as to be recognized by the T lymphocytes of the host. They do not stimulate the production of antibodies because B cells may not be adapted to the recognition of a very low density of antigenic peptides bound to class I molecules" (see page 26, column 2, paragraph 2). "Are the TSTA like tum- antigens, the result of mutations occurring throughout the genome? Certainly, the large diversity of TSTA would be consistent with this notion" (see page 26, column 2, paragraph 3). "It would also imply that the TSTA bear no functional relation with the cellular modifications that lead to malignant transformation" (see page 27, column 1). "Only the cloning of the relevant genes and comparison of their sequences with those found in normal cells can give a complete answer to the problem. Thus, for man, the genetic approach probably will be required not only to establish the nature of TSTA but also to demonstrate their existence" (page 28, column 1).

Therefore, the skilled artisan recognized the difficulty in defining or enabling a human tumor antigen, regardless of the type of tumor antigen (e.g tum- antigens, TSTA, MAGE), whether it was at the time the invention was made and recognized the requirement to demonstrate its existence by trial and error and undue experimentation.

Here, the specification does not provide sufficient enablement of a genus of MAGE tumor rejection antigen precursor proteins based upon the limited disclosure/recitation of a one nucleic acid encoding MAGE-1 or upon the limited information (nucleic acids but not cDNA sequences or amino acid sequences nor isolation of MAGE TRAP protein) on each one of MAGE 1-11 TRAP proteins that can be isolated from melanoma cells. There is insufficient direction and guidance as to the discrete structure / sequences of nucleic acids or which the complementary sequence can hybridize to SEQ ID NO: 8 and encode a genus of diverse tumor rejection antigen precursors and, in turn, provide the appropriate structural, expression and functional attributes of a genus of tumor antigen precursors, with distinct structural, expression and functional properties.

Further, given the inability of each species of the disclosed MAGE 1-11 to satisfy the four criteria of TRAPs (see above) as well as the diversity of structure of the members of the MAGE family (e.g. MAGE 2-6 and 8-12 have 57% - 77% amino acid identity with MAGE-1; see page 365, column 1, paragraph 1 of **De Plaen et al**.); there is an insufficient enabling disclosure of a genus of MAGE tumor rejection antigen precursor proteins encoded by nucleic acids the complement of which hybridizes to SEQ ID NO: 8 under the enablement provision of 35 USC 112, first paragraph.

The specification does not provide a sufficient enabling description of the claimed invention. A person of skill in the art is not enabled to make and use any MAGE TRAP protein as recited in the claims. A person of skill in the art would not know which nucleic acid or amino acid sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences (e.g. tumor rejection antigens / TRAs that stimulate cytotoxic T lymphocytes). There is insufficient guidance based on identifying hybridizing nucleic acids and certain assays of a limited number of species (e.g. MAGE-1, -2, -3) to direct a person of skill in the art to select particular nucleic acid or amino acid sequences as essential for identifying a MAGE TRAP protein, for the expression of a MAGE TRAP protein on cancer cells and for those MAGE TRAP protein-derived TRA sequences essential for stimulating cytotoxic T lymphocytes, including vaccine compositions. A person of skill in the art could not predict which particular amino acid sequences of MAGE TRAP proteins are essential and could be used in stimulating cytotoxic T lymphocytes, including as vaccine compositions.

Nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8 do not provide a sufficient enabling disclosure under 35 USC 112, first paragraph for a genus of diverse tumor rejection antigen precursors, particularly the four characteristics *(i)* – *(iv)* for MAGE TRAP proteins.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 to any or all of the TRAP properties *(i)* – *(iv)* outlined above.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 and MAGE TRAP protein expression itself or expression of a MAGE TRAP protein on a cancer cell.

For example, the disclosed MAGE-7 has not been found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes (see page 365, column 1, paragraph 1 of **De Plaen et al**).

The structure of genes MAGE-5 and 7-11 have not been completely defined because no cDNA clones have obtained at least up to the 1994 publication date of **De Plaen et al.** (see page 364, column 2, first full paragraph of **De Plaen et al.)**.

Again, as indicated above, the specification as-filed does not provide for the cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein itself for each of the 11 species of MAGE 1-11 in the specification as-filed.

Also, there is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 and the tumor rejection antigens (TRAs) or peptides which complex to MHC molecules to form targets for CTLs.

There is insufficient correlation of the structure of SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 to the immunogenicity of MAGE TRAP proteins or to the TRAs that are complexed to MHC molecules to form targets for CTLs.

The specification does not provide sufficient guidance and direction correlating structure to function for identifying the relevant structural characteristics that are coupled with a MAGE TRAP protein that satisfies the four characteristics (see *TRAP characteristics (i), (ii), (iii), (iv)*), of a MAGE TRAP protein, including a genus of MAGE tumor rejection antigen precursor proteins encoded by nucleic acids the complement of which hybridizes to SEQ ID NO: 8 under the enablement description provision of 35 USC 112, first paragraph.

Because of the lack of sufficient guidance and predictability in determining on how to make and use any MAGE TRAP protein, it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of MAGE TRAP proteins that satisfies the four characteristics (see *TRAP characteristics (i), (ii), (iii), (iv)*), of a MAGE TRAP protein is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

**(11) Response to Argument**

Prior to the Response to Appellant's Arguments, the following is noted.

Appellant relies upon Hogan, 194 USPQ 527 (CCPA 1977) and In re Koller et al., 204 USPQ 702 (CCPA 1980) to argue that as a matter of law, reliance upon post-filing date references has been improper to determine the scope of enablement and the description requirement under 35 USC 112, first paragraph.

However, as noted at page 706 in In re Koller et al., the Court recognized that later-issued patents and publications may be used to show the state of the art existing on the date the application in question.

As noted in Footnote 5 on page 707 in In re Koller et al., The circumstances listed in In re Hogan at page 537 were as follows:

"Where, for example, a later publication evidenced that, as of an application's filing date, undue experimentation would have been required, ... or that a parameter absent from the claims was or was not critical, .... or that a statement in the specification was inaccurate, ... or that the invention was inoperative or lacked utility, ... or that a claim was indefinite, ... , or that characteristics of prior art products were known ..." .

As stated in In re Wright 27 USPQ2d 1510, 1512 (CAFC 1993), the issue is not what the state of the art is today or what a skilled artisan today would believe, but rather what the state of the art at the time of filing and what a skilled artisan would have believed at that time. Hybritech Inc. v. Monoclonal Antibodies, Inc. 802 F2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir.), cert denied, 480 U.S. 947 (1987); In re Hogan, 559 F2d 595, 604, 194 USPQ 527, 535 (CCPA 1977).

A specification must be enabling as of the filing date. It is noted that post-filing date references can be used as evidence of the state of the art existing on the filing date of the application. See MPEP 2164.05(a), including In re Hogan , 194 USPQ 527 (CCPA 1977) and In re Wright , 27 USPQ2d 1510 (Fed. Cir. 1993).

Further, it is noted that the enablement determination is made retrospectively, by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time. See Enzo Biochem Inc. v. Calgene Inc. 52 USPQ2d 1129 (CAFC 1999).

With respect to appellant's comments on the Examiner's use of references that "postdate" appellant's effective filing date, such references are appropriate to serve as published art-recognized references to support the Examiner's position in the rejection and for showing the state of the art with regards to particular problems or known facts that indicate that address issues under 35 USC 112, first paragraph, written description and enablement

**Rejection Under 35 U.S.C. 112, First Paragraph, Written Description**

**(A) Appellant Asserts That The Rejection of Claims 183, 185, 186, 188, 189 and 198 for Failing to Satisfy the Written Description Requirement of 35 USC 112, first paragraph is Erroneous and Should be Reversed.**

Appellant's arguments have been fully considered but have not been found convincing.

Analysis with respect to the following **characteristics of MAGE TRAPs** follows.

***(i) MAGE TRAPS are proteins that are encoded by naturally occurring non-mutagenized genes.***

***(iii) MAGE TRAPS are all encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions.***

Appellant notes that a gene family was suggested by the data, which included Southern Blotting and hybridization under stringent conditions (e.g. see Examples 23 and 29 of the specification).

Appellant notes that information on some of these MAGE coding sequences are provided in Figure 13 of the application.

In addition, appellant notes that the disclosed experiments show no expression of MAGE 1-3 in normal tissues (except for testis) coupled with expression in cancer cells (see Figures 11A and 11B).

Appellant submits that the disclosed Examples provide 11 species that satisfy the claim limitations.

Appellant admits that the MAGE molecules differ from each other as members of a genus do. Appellant notes that the members are similar to each other, such that their complements hybridize to each other under stringent conditions. Appellant submits that similarity is not identity, however when nucleic acid molecules share a common structural feature, their complements will hybridize to each other, which is the common structural feature uniting what is claimed.

Although appellant does not disagree that MAGE-1 can be polymorphic in response to issues raised in the rejection of record, several lines of evidence suggest that MAGE genes show little variation or polymorphism from one individual to another (see page 365, column 2, paragraph 1 of **De Plaen et al.**).

In terms of written description, appellant submits that the issue is whether the specification adequately described the claimed diversity or polymorphisms which fall under the language of the stringent conditions of hybridization. Appellant submits that the specification does describe said diversity or polymorphisms via hybridization with SEQ ID NO: 8 at the recited conditions.

Appellant submit that PCR permits differentiation among the MAGE family members, even if Northern Blotting does not, as indicated by Brasseur et al., Int. J. Cancer 52: 839-841 (1992), of record.

It is acknowledged that the sequences of the MAGE genes do not show significant homology with known sequences in the databases (see page 365, column 1, lines 2-4 below Figure 4 of **De Plaen et al.**).

Also, it is acknowledged that probing cosmid libraries with a MAGE-1 sequence, 11 closely related genes have been identified in the specification as filed (see the instant specification and **De Plaen et al.,** particularly the Abstract and Discussion).

As noted in the Brief, "Applicant admit the molecules differ from each other. Members of a genus do. They are similar to each other, such that their complements hybridize to each other under stringent conditions. Similarity is not identity, however, when nucleic acid molecules share common structural features, their complements will hybridize to each other. This is in fact a common structural feature."

As noted above with respect to *(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions*, the claims do not recite all of the stringent conditions set forth on pages 49-50 in Example 32, as asserted and relied upon by appellant.

However, as indicated above and reiterated herein, appellant's assertions that the disclosed Examples provide 11 species that satisfy the *characteristics* or claim limitations of MAGE TRAP proteins are not consistent with the disclosure of the instant application as filed nor with synopsis of the MAGE family in **De Plaen et al.** (Immunogenetics 40: 360-369, 1994).

The claims are drawn to MAGE TRAP proteins and not nucleic acids.

The instant specification does not provide for the isolation of a representative protein for each family member of MAGE 1-11 TRAPs.

The instant specification does not provide for the cDNA nor the amino acid sequence for each family member of MAGE 1-11 TRAPs.

The instant specification does not provide the structural diversity of the proteins (i.e. amino acids) encompassed by the claimed MAGE TRAPs.

For example, the MAGE genes have their entire coding sequence located in the last exon, which shows 64 - 85% nucleic acid identity with that of MAGE-1 (see entire document of **De Plaen et al.,** particularly the Abstract and Discussion).

The structure of genes MAGE-5 and 7-11 have not been completely defined because no cDNA clones have obtained up to now (see page 364, column 2, first full paragraph of **De Plaen et al**.).

MAGE-2-6 and 8-12 proteins have 57% - 77% amino acid identity with MAGE-1 (see page 365, column 1, paragraph 1 of **De Plaen et al.**).

Again, it is noted that in the publication by **De Plaen et al.**, MAGE-7 was not included for comparison, because it was not found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes.

While the instant specification discloses 11 closely related MAGE genes that have been identified by probing cosmid libraries with a MAGE-1 sequence, the application as-filed did not provide a sufficient disclosure of sufficiently, detailed, relevant identifying characteristics which provide evidence that appellant was in possession of the claimed invention of MAGE TRAP proteins that satisfy the *TRAP characteristics*. The disclosure must show that the inventor has invented each feature that is included in a claim limitation. Appellant must convey with reasonable clarity to those skilled in the art that as of the filing date sought, he or she was in possession of the invention. One does need to be able to describe the invention with particularity.

Adequate written description require a precise definition, such as structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention. Appellant has not satisfied the written description of the MAGE TRAP genus of polypeptides in the absence of a disclosed correlation to a structure and possessed a sufficient number of species that satisfy the *MAGE TRAP protein characteristics* asserted by appellant.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 itself, much less, nucleic acids hybridizing to SEQ ID NO: 8, and any or all of the *TRAP properties* outlined above.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 and MAGE TRAP protein expression itself or expression of a MAGE TRAP protein.

For example, the disclosed MAGE-7 has not been found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes (see page 365, column 1, paragraph 1 of **De Plaen et al**).

The structure of genes MAGE-5 and 7-11 have not been completely defined because no cDNA clones have obtained at least up to the 1994 publication date of **De Plaen et al.** (see page 364, column 2, first full paragraph of **De Plaen et al.)**.

Again, as indicated above, the specification as-filed does not provide for the cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein itself for each of the 11 species of MAGE 1-11 disclosed in the specification as filed.

Importantly, it is noted that claims are not even limited to SEQ ID NO: 8 itself, but rather encompass nucleic acid molecules that hybridize to SEQ ID NO: 8, thereby a greater diversity of nucleic acid sequences and, in turn, a greater diversity of amino acid sequences encoding a MAGE TRAP protein are encompassed by the claims.

As appellant acknowledges, the hybridization language provides for a diversity of nucleic acids and, in turn, a diversity of amino acids and MAGE TRAP proteins. Such hybridization language encompass distinct MAGE TRAP nucleic acid and, in turn, MAGE TRAP proteins, each of which differ with respect to the *MAGE TRAP characteristics* relied upon by appellant.

For example, even if one nucleotide is deleted or inserted at a single place within the nucleic acid sequence, all the codons downstream of that insertion or deletion will be frame shifted, which can result in a protein that differs in both structure and function with the referenced encoding sequence. Such issues have occurred in the instant application in that the originally filed SEQ ID NOS: 7 and 8 presented errors in that they were missing a single nucleotide base, a "C", following nucleotides 1377 ( SEQ ID NO: 7) and 4633 (SEQ ID NO: 8). See appellant's Declaration, filed 7/9/98, particularly Paragraph 2 and appellant's Declaration, filed 7/10/2000, including paragraph 10. Although appellant has corrected SEQ ID NOS: 7 and 8 in the instant application, this evidence does show that possession of a correct sequence was not necessarily readily apparent.

The claimed hybridization conditions to a referenced nucleic acid does not result in MAGE TRAP proteins that have all of the identifiable properties or *TRAP characteristics* of MAGE-1 or a MAGE TRAP protein, as evidenced above.

While appellant relies upon hybridizing nucleic acids as the key common structural feature, the specification as-filed does not account for the distinguishing structural, expression and functional characteristics of each of the 11 MAGE TRAP species, not all of which meet the critical *characteristics of MAGE TRAPs* asserted in the Brief.

Written description requires for the functional characteristics *(*see *TRAP characteristics)* of a MAGE TRAP protein to be coupled with a disclosed correlation to a structure (i.e. nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8). Sufficient disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described rather than merely describing the claimed subject matter in functional terms as a MAGE TRAP protein which are encoded by nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8.

***(ii) MAGE TRAPs are characteristic of cancer cells, and are not expressed by normal cells (with the exception of testis cells).***

Appellant's arguments that the Examples provide 11 species that satisfy the claim limitations have been fully considered but have not been found convincing.

In contrast to appellant's assertions that the disclosed Examples provide 11 species that satisfy the claim limitations, the following is noted.

It is acknowledged that none of the MAGE genes were expressed in a large panel of healthy tissues, with the exception of testis and placenta. (see Abstract and Expression of MAGE genes on pages 366-367 of **De Plaen et al.**).

However, the instant specification does not provide for the expression of each of the disclosed MAGE 1-11 TRAP proteins on cancer cells.

For example, the instant specification does not appear to provide for the expression of MAGE 5-11 either at the nucleic acid or protein level in/on normal and cancer cells.

Upon further investigation by the co-inventors, six genes of the MAGE family (MAGE-1, -2, -3, -4, -6 and -12) have been found to be expressed in a number of tumors of various histological types (see Abstract and Expression of MAGE genes on pages 366-367 of **De Plaen et al**.).
Again, Note MAGE-12, which cited by De Plaen et al., was not disclosed in the specification as-filed

MAGE-5, -8, -9, -10 and -11 were very weakly expressed in all samples that have been examined (see page 367, column 1, paragraph 2 of **De Plaen et al**.). .

Again, the disclosed MAGE-7 has not been found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes (see page 365, column 1, paragraph 1 of **De Plaen et al**).

There is insufficient objective evidence to establish the nexus betwen SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 themselves and any or all of the MAGE TRAP protein properties outlined above.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 themselves and MAGE TRAP protein expression on a cancer cell obtainable from a melanoma, given that not all of the disclosed MAGE 1-11 is expressed (e.g MAGE-7) or expressed on a cancer cell at a significant level (e.g. MAGE-5, -8, -9, -10 and –11).

***(iv) MAGE TRAPS are processed, intracellularly, into TRAs (tumor rejection antigens), i.e., peptides, which complex to MHC molecules to form targets for cytotoxic T lymphocytes (CTLS).***

Appellant's arguments that the Examples provide 11 species that satisfy the claim limitations have been fully considered but have not been found convincing.

In contrast to appellant's assertions that the disclosed Examples provide 11 species that satisfy the claim limitations, the following is noted.

Given the conservation of sequences in MAGE genes, it has been suggested that the proteins produced by all of these genes may exert very similar functions. At the time the invention was made and post-filing, there was no indication regarding this function (page 367, column 2, paragraph 3 of **De Plaen et al.).**

It is likely that various regions of the different MAGE proteins can contribute peptides combining with various HLA class I molecules (page 368, column 1, paragraph 2 of **De Plaen et al.**).

This was consistent with the specification as-filed which describes on page 55, paragraph 1 of the specification, which makes clear that the sequences code for **tumor rejection antigen precursors (TRAPS** which, in turn are processed into **tumor rejection antigens (TRAs)**. The evidence points to presentation of TRAs on tumor cells, followed by the development of an immune response and deletion of the cells. TRAPS which are processed into TRAs and the TRAs themselves may be used either alone or in pharmaceutically appropriate compositions as vaccines.

The function of a MAGE TRAP protein to contribute peptides combining with various HLA class I molecules or as a source of a vaccine has not been solely based on the determination that nucleic acids that hybridize with SEQ ID NO: 8 have been identified, on the determination that a MAGE TRAP protein itself may or may not be isolated or on the determination that a MAGE TRAP protein may or may not be expressed on a cancer cell.

Rather, the function of a MAGE TRAP protein rests on its ability to be processed, intracellularly, into TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs, which needs to be tested empirically

Even the known MAGE molecules exhibit extremely low immunogenicity and initiation of a strong immune response to tumor antigens is vivo is an extremely rare event (see page 674, paragraph 2 of Kirkin et al., APMIS 106: 665-679, 1998).

Therefore, the reliance upon the function of the claimed tumor rejection antigen precursors depends, in part, upon the antigen processing and presentation of MAGE-derived peptides, which, in turn, can form targets for cytotoxic T cells directed against these peptides.

While such efforts may provide the groundwork for determining a MAGE tumor antigen precursor, "it is difficult to predict whether therapeutic success will be achieve, even if a significant increase in anti-tumor cytotoxic lymphocytes is obtained by immunization" (see Boon et al. (Int. J. Cancer 54: 177-180, 1993; see page 178, column 2, paragraph 2).

Further, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

The specification as-filed does not provide for the tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs), other than than the disclosure that SEQ ID NO: 26 for MAGE-1 which can be presented to anti-E CTL (see Example 34 on pages 50-51 of the instant specification). This was accomplished by screening synthetic peptides derived from exon 3.1 to determine which if any of the peptides could confer sensitivity to anti-E CTL. Again, presentation of TRAs from MAGE-1 needed to be tested empirically.

The only HLA molecule acsociation disclosed in the specification as-filed was the presentation of the antigen MZ2-E to autologous CTL via HLA A-1 (see Example 26 on pages 45-46 of the instant specification).

The instant specification does not appear to provide for the ability of MAGE 4-11 transfectants to stimulate cytotoxic T lymphocytes.

The instant specification does not appear to provide for the cytotoxic T lymphocytes (CTLs) to test the properties of MAGE 4-11 as MAGE TRAP proteins.

Even with respect to MAGE-2 and –3, it is not readily apparent that the specification as-filed provides tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs or for the cytotoxic T lymphocytes (CTLs) to test the properties of MAGE-2 and –3 as MAGE TRAP proteins.

Although appellant has argued and distinguished between different classes of tumor or tumor-associated antigens (e.g. tum$^-$ and TSTA) in defining the MAGE family encompassed by the claimed invention, the reliance on the teachings of Stevenson and Boon, in part, was to show that defining or possessing human tumor antigens, including human tumor antigens, that result in stimulating cytotoxic T lymphocytes to tumors was difficult at the time the invention was made.

Although appellant asserts that the degree of immunogenicity is a not a feature of the claims and therefore irrelevant, appellant is reminded of element *(iv) MAGE TRAPS are processed, intracellularly, into TRAs (tumor rejection antigens), i.e., peptides, which complex to MHC molecules to form targets for CTLS* relied upon by appellant in characterizing MAGE TRAP proteins.

With respect to the attachment to the Brief, appellant provision of a partial Listing of the literature on MAGE TRAPs showing that the molecules are, in fact, immunogenic is acknowledged.

Written description requires for the functional characteristics of a MAGE to be coupled with a disclosed correlation to a structure (i.e. nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8). Sufficient disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described rather than merely describing the claimed subject matter in functional terms as a MAGE TRAP which are encoded by nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8.

As pointed out above, the specification as filed does not provide for the tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs), other than the specific peptide SEQ ID NO: 26 (EADPTGHSY) which forms a complex with HLA-A1 and stimulates proliferation of CTLs and which is specific for MAGE-1.

In addition to the lack of written support for the immunogenic peptides provided with the Brief in the specification as-filed, the specification as-filed did not provide written description for the various HLA molecules referenced in this listing. Again, the specification as-filed only provided written support for the specific peptide SEQ ID NO: 26 (EADPTGHSY), which forms a complex with HLA-A1.

The specification as-filed does not provide for the cDNA nor the amino acid sequences as well as isolation for each of the MAGE 1-11 disclosed in the specification as filed.

Given the absence of providing sufficient information (e.g. cDNA or amino acid sequence) concerning MAGE TRAP proteins, the specification as-filed did not provide a sufficient correlation between a particular MAGE TRAP protein and its associated tumor rejection antigens (TRAs) which complex to different MHC molecules to form targets for CTLs.

As indicated above, the specification as-filed did not provide for the cytotoxic T lymphocytes (CTLs) to test the properties of each of MAGE 1-11.

With respect to the reliance of the claimed MAGE tumor rejection antigen precursors proteins on antigen processing and presentation and recognition by cytototoxic T cells directed against peptides derived from said MAGE proteins, it is acknowledged that cytotoxic T cells can be used in vitro rather than in vivo in response to appellant's comments.

**B) Appellant Asserts That The Rejection of Claims 184, 187 and 190 for Failing to Satisfy the Written Description Requirement of 35 USC 112, first paragraph is Erroneous and Should be Reversed**

Appellant notes that each of claims 184, 187 and 190 required that the MAGE tumor rejection antigen precursor includes the nine amino acid sequence of SEQ ID NO: 26, which has been shown to function as a tumor rejection antigen which forms a complex with HLA-A1 molecules an stimulates proliferation of cytotoxic T lymphocytes (CTLs) (see U.S. Patent No. 5,925,729 and Example 34 of the instant specification).

Appellant asserts that the claims require a commonality of structure and that the USPTO has accepted the proposition that SEQ ID NO: 26 is a tumor rejection antigen (TRA).

However, appellant has not provided for a nucleic acid or an amino acid that encodes a MAGE TRAP protein other than MAGE-1 itself (encoded by SEQ IDNO: 8) that when processed can result in the stimulation of a CTL that recognizes the specific peptide SEQ ID NO: 26.

As indicated, in part, above in Section (A), the specification does not provide for the cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein other than MAGE-1 itself (encoded by SEQ ID NO: 8) that can provide for the antigen presentation of SEQ ID NO: 26 to CTLs.

The claims are not limited to MAGE-1.

Further, the specification as filed does not even provide for the structure and diversity of MAGE-1.

As pointed out above, the specification as filed does not provide for the tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs), other than the specific peptide SEQ ID NO: 26 (EADPTGHSY) which stimulates proliferation of CTLs and which is specific for MAGE-1.

According to the Listing of TRAPS submitted with the Brief, it appears that SEQ ID NO: 26 (EADPTGHSY) of MAGE-1 can complex with HLA B35. However, the specification as-filed does not provide a written description for this observation that MAGE-1 derived peptides can complex with HLA molecules other than HLA-A1.

As disclosed on page 30, paragraph 2 of the instant specification, in isolating the pertinent nucleic acid sequence for a tumor rejection antigen precursor, the techniques developed by appellant showed that a recipient cell is needed which fulfills two criteria: (i) the recipient cell must not express the TRAP of interest under normal conditions, and (ii) it must express the relevant class I HLA molecule.

Therefore, it was necessary to have the appropriate CTLs readily available and know what was the relevant class I HLA molecule associated with each MAGE TRAP protein in order to determine whether a MAGE TRAP protein satisfied the four criteria *(i) – (iv)* for a MAGE TRAP.

Consistent with the specification as filed and appellant's arguments, it is likely that various regions of the different MAGE proteins can contribute peptides combining with various HLA class I molecules (page 368, column 1, paragraph 2 of **De Plaen et al.**).

The specification as-filed does not appear to provide for a CTL to test whether MAGE-1 TRAP protein or a MAGE TRAP protein comprising SEQ ID NO: 26 can complex with HLA B35, as relied upon by appellant in providing the listing of TRAP immunogenic peptides.

In addition to the lack of written support for the immunogenic peptides provided with the Brief in the specification as-filed, the specification as-filed did not provide written description for the various HLA molecules referenced in this Listing of TRAPS. Again, the specification as-filed only provided written support for the specific peptide SEQ ID NO: 26 (EADPTGHSY), which forms a complex with HLA-A1.

In contrast to the Listing of TRAPS provided in the Brief, the disclosure of a single peptide obtained from MAGE-1 and its association with HLA-A1 in the specification as-filed does not provide for a sufficient number of species of TRAs or their association with specific MHC molecules to satisfy the genus of MAGE TRAP proteins, encompassed by the claims.

The specification as-filed does not provide for the cDNA nor the amino acid sequences as well as isolation for each of the MAGE 1-11 disclosed in the specification as filed.

Given the absence of providing sufficient information (e.g. cDNA or amino acid sequence) concerning MAGE TRAP proteins, the specification as-filed did not provide a sufficient correlation between a particular MAGE TRAP protein and its associated tumor rejection antigens (TRAs) which complex to different MHC molecules to form targets for CTLs.

As noted above, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

Given that the claims encompass nucleic acids that hybridize to SEQ ID NO: 8 and Given that "variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2 or Kirkin et al.), appellant was not in possession of a genus of MAGE TRAP proteins comprising SEQ ID NO: 26 wherein the MAGE TRAP protein relies upon nucleic acids that hybridize to SEQ ID NO: 8. Given the hybridization language encompassed by the claims, the claimed MAGE TRAP proteins comprise variations in amino acid sequences. Therefore, there is insufficient evidence that appellant was in possession of a genus of MAGE TRAP proteins comprising SEQ ID NO: 26 that would provide SEQ ID NO: 26 itself and, more importantly, provide SEQ ID NO: 26 that is recognized by an appropriate CTL.

Written description requires for the functional characteristics *(see TRAP characteristics)* of a MAGE TRAP protein to be coupled with a disclosed correlation to a structure (i.e. nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8). Sufficient disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described rather than merely describing the claimed subject matter in functional terms as a MAGE TRAP protein which are encoded by nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8 wherein the isolated TRAP comprises SEQ ID NO: 26.

**C) Examiner Submits That The Rejection of Claims 189-191 for Failing to Satisfy the Written Description Requirement of 35 USC 112, first paragraph Should Stand or Fall Together**

As described on page 55, paragraph 1 of the specification, the disclosure make clear that the sequences code for **tumor rejection antigen precursors (TRAPS** which, in turn are processed into **tumor rejection antigens (TRAs)**. The evidence points to presentation of TRAs on tumor cells, followed by the development of an immune response and deletion of the cells. TRAPS which are processed into TRAs and the TRAs themselves may be used either alone or in pharmaceutically appropriate compositions as vaccines.

The following definition of a vaccine is found on page 309 of the Illustrated Dictionary of Immunology, Cruse and Lewis, CRC Press, Boca Raton, FL, 1994.

Vaccine: Live attenuated or killed organisms or parts or products from them which contain antigens that can stimulate a specific immune response consisting of protective antibodies and T cell immunity. A vaccine should stimulate a sufficient number of memory T and B lymphocytes to yield effector T cells and antibody-producing B cells from memory cells. It should also be able to stimulate high titers of neutralizing antibodies. Invention of a vaccine into a nonimmune subject induces active immunity against the modified pathogens.

As indicated, in part, above in Sections (A) and (B), the specification does not provide for the cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein other than MAGE-1 itself that can provide for the antigen presentation to CTLs and, in turn, serve as a vaccine.

As indicated, in part, above in Sections (A) and (B) with respect to MAGE tumor antigen precursors, "it is difficult to predict whether therapeutic success will be achieve, even if a significant increase in anti-tumor cytotoxic lymphocytes is obtained by immunization" (see Boon et al. (Int. J. Cancer 54: 177-180, 1993; see page 178, column 2, paragraph 2).

Further, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

The claims are not limited to those MAGE TRAP proteins that have been shown to be sufficiently immunogenic to serve as a vaccine.

Further, the specification as filed does not provide for the structure and diversity of MAGE TRAPs and their ability to serve as a vaccine.

As indicated above, not each one of MAGE 1-11 disclosed in the specification as filed is expressed on a cancer cell.

Nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8 do not provide sufficient written description provision of 35 USC 112, first paragraph for a genus of diverse tumor rejection antigen precursors, including the four characteristics for MAGE TRAPS, particularly the ability of the genus of MAGE TRAPS to serve as a vaccine.

The instant specification does not appear to provide for a genus of MAGE tumor rejection antigen precursor proteins that are expressed on cancer cells and, in turn, can serve as a vaccine, such as providing tumor rejection antigens (TRAs) for the antigen presentation to CTLs.

As disclosed on page 30, paragraph 2 of the instant specification, in isolating the pertinent nucleic acid sequence for a tumor rejection antigen precursor, the techniques developed by appellant showed that a recipient cell is needed which fulfills two criteria: (i) the recipient cell must not express the TRAP of interest under normal conditions, and (ii) it must express the relevant class I HLA molecule.

Consistent with the specification as filed and appellant's arguments, it is likely that various regions of the different MAGE proteins can contribute peptides combining with various HLA class I molecules (page 368, column 1, paragraph 2 of **De Plaen et al.**).

Therefore, it was necessary to have the appropriate CTLs readily available and know what was the relevant class I HLA molecule associated with each MAGE TRAP protein in order to determine whether a MAGE TRAP protein satisfied the four criteria *(i) – (iv)* for a MAGE TRAP.

The specification as-filed does not appear to provide for a CTL to test whether MAGE-1 TRAP protein or a MAGE TRAP protein comprising SEQ ID NO: 26 can complex with HLA B35, as relied upon by appellant in providing the listing of TRAP immunogenic peptides.

In addition to the lack of written support for the immunogenic peptides provided with the Brief in the specification as-filed, the specification as-filed did not provide written description for the various HLA molecules referenced in this listing. Again, the specification as-filed only provided written support for the specific peptide SEQ ID NO: 26 (EADPTGHSY) which forms a complex with HLA-A1.

The specification as-filed does not provide for the cDNA nor the amino acid sequences as well as isolation for each of the MAGE 1-11 disclosed in the specification as filed.

Given the absence of providing sufficient information (e.g. cDNA or amino acid sequence) concerning MAGE TRAP proteins and empirical evidence to support the vaccine claim limitations, the specification as-filed did not provide a sufficient correlation between a particular MAGE TRAP protein and its associated tumor rejection antigens (TRAs) which complex to different MHC molecules to form targets for CTLs and, in turn, result in protective immune responses.

**Rejection Under 35 U.S.C. 112, First Paragraph, Enablement**

**(A) Appellant Asserts That The Rejection of Claims 183, 185, 186, 188, 189 and 198 for Failing to Satisfy the Enablement Requirement of 35 USC 112, first paragraph is Erroneous and Should be Reversed**

Appellant's arguments have been fully considered but have not been found convincing.

Analysis with respect to the following characteristics of MAGE TRAPs follows.

***(i) MAGE TRAPS are proteins that are encoded by naturally occurring non-mutagenized genes.***

***(iii) MAGE TRAPS are all encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions.***

Appellant notes that a gene family was suggested by the data, which included Southern Blotting and hybridization under stringent conditions (e.g. see Examples 23 and 29 of the specification).

Appellant notes that information on some of these MAGE coding sequences are provided in Figure 13 of the application.

In addition, appellant notes that the disclosed experiments show no expression of MAGE 1-3 in normal tissues (except for testis) coupled with expression in cancer cells (see Figures 11A and 11B).

Appellant submits that the disclosed Examples provide 11 species that satisfy the claim limitations.

Appellant admits that the MAGE molecules differ from each other as members of a genus do. Appellant notes that the members are similar to each other, such that their complements hybridize to each other under stringent conditions. Appellant submits that similarity is not identity, however when nucleic acid molecules share a common structural feature, their complements will hybridize to each other, which is the common structural feature uniting what is claimed.

Although appellant does not disagree that MAGE-1 can be polymorphic in response to issues raised in the rejection of record, several lines of evidence suggest that MAGE genes show little variation or polymorphism from one individual to another (see page 365, column 2, paragraph 1 of **De Plaen et al.**).

Appellant submits that the specification does describe said diversity or polymorphisms via hybridization with SEQ ID NO: 8 at the recited conditions and that it is not uncommon to define nucleic acid molecules structurally, by means of their ability to hybridize to specific molecules.

Appellant submit that PCR permits differentiation among the MAGE family members, even if Northern Blotting does not, as indicated by Brasseur et al., Int. J. Cancer 52: 839-841 (1992), of record.

It is acknowledged that the sequences of the MAGE genes do not show significant homology with known sequences in the databases (see page 365, column 1, lines 2-4 below Figure 4 of **De Plaen et al.**).

Also, it is acknowledged that probing cosmid libraries with a MAGE-1 sequence, 11 closely related genes have been identified in the specification as filed (see the instant specification and **De Plaen et al.,** particularly the Abstract and Discussion).

However, as indicated above and reiterated herein, appellant's assertions that the disclosed Examples provide 11 species that satisfy the four characteristics or claim limitations of MAGE TRAP proteins are not consistent with the disclosure of the instant application as filed nor with synopsis of the MAGE family in **De Plaen et al.** (Immunogenetics 40: 360-369, 1994).

The claims are drawn to MAGE TRAP proteins and not nucleic acids.

The instant specification does not provide for the isolation of a representative protein for each family member of MAGE 1-11 TRAPs.

The instant specification does not provide for the cDNA nor the amino acid sequence for each family member of MAGE 1-11 TRAPs.

The instant specification does not provide the structural diversity of the proteins (i.e. amino acids) encompassed by the claimed MAGE TRAPs.

For example, the MAGE genes have their entire coding sequence located in the last exon, which shows 64 - 85% nucleic acid identity with that of MAGE-1) and most of the putative MAGE proteins are 309-319 amino acids long (see entire document of **De Plaen et al.,** particularly the Abstract and Discussion).

The structure of genes MAGE-5 and 7-11 have not been completely defined because no cDNA clones have obtained up to now (see page 364, column 2, first full paragraph of **De Plaen et al**.).

MAGE-2-6 and 8-12 proteins have 57% - 77% amino acid identity with MAGE-1 (see page 365, column 1, paragraph 1 of **De Plaen et al.**).

Again, it is noted that in the publication by **De Plaen et al**., MAGE-7 was not included for comparison, because it was not found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes.

The teachings in the specification provide for a plan or an invitation to the skilled artisan to experiment practicing the claimed but do not provide sufficient guidance and specificity how to apply detailed, relevant identifying characteristics in making and using MAGE TRAP proteins that satisfy the TRAP characteristics in order to execute that plan.

In support of the unpredictability of the claimed genus of MAGE TRAP proteins, the evidence supports the contention that strategies drawn to isolating and determining a MAGE TRAP protein that satisfies the TRAP characteristics have not been universally straightforward or as easy to apply as was initially hoped or disclosed in the specification as-filed nor has the interpretation of results always been unambiguous.

The diversity of structure, expression and function as a MAGE TRAP of the disclosed MAGE 1-11 is consistent with a recurring problem when a specificaton sets forth a single or a limited number of examples in an effort to be enabling of broad claims. Here, the claims are drawn to biological systems which are generally considered unpredictable and which need to be tested by trial and error, resulting in undue experimentation.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 itself, much less, nucleic acids hybridizing to SEQ ID NO: 8, and any or all of the *TRAP properties* outlined above.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 or nucleic acids that hybridize to SEQ ID NO: 8 and protein expression itself or expression on a cancer cell.

For example, the disclosed MAGE-7 has not been found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes (see page 365, column 1, paragraph 1 of **De Plaen et al**).

The structure of genes MAGE-5 and 7-11 have not been completely defined because no cDNA clones have obtained at least up to the 1994 publication date of **De Plaen et al.** (see page 364, column 2, first full paragraph of **De Plaen et al.)**.

Again, as indicated above, the specification as-filed does not provide for the cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein itself for each of the 11 species of MAGE 1-11 disclosed in the specification as filed.

Importantly, it is noted that claims are not even limited to SEQ ID NO: 8 itself, but rather encompass nucleic acid molecules that hybridize to SEQ ID NO: 8, thereby a greater diversity of nucleic acid sequences and, in turn, a greater diversity of amino acid sequences encoding a MAGE TRAP protein are encompassed by the claims.

As noted in the Brief, "Applicant admit the molecules differ from each other. Members of a genus do. They are similar to each other, such that their complements hybridize to each other under stringent conditions. Similarity is not identity, however, when nucleic acid molecules share common structural features, their complements will hybridize to each other. This is in fact a common structural feature."

As noted above with respect to *(iii) they are encoded by nucleic acid molecules which hybridize to a reference sequence, i.e. one which encodes MAGE-1 (SEQ ID NO: 8), under strictly defined, stringent conditions*, the claims do not recite all of the stringent conditions set forth on pages 49-50 in Example 32, as asserted and relied upon by appellant.

As appellant acknowledges, the hybridization language provides for a diversity of nucleic acids and, in turn, a diversity of amino acids and MAGE TRAP proteins. Such hybridization language encompass distinct MAGE TRAP nucleic acid and, in turn, MAGE TRAP proteins, each of which differ with respect to the *MAGE TRAP characteristics* relied upon by appellant.

For example, even if one nucleotide is deleted or inserted at a single place within the nucleic acid sequence, all the codons downstream of that insertion or deletion will be frame shifted, which can result in a protein that differs in both structure and function with the referenced encoding sequence. Such issues have occurred in the instant application in that the originally filed SEQ ID NOS: 7 and 8 presented errors in that they were missing a single nucleotide base, a "C", following nucleotides 1377 ( SEQ ID NO: 7) and 4633 (SEQ ID NO: 8). See appellant's Declaration, filed 7/9/98, particularly Paragraph 2 and appellant's Declaration, filed 7/10/2000, including paragraph 10. Although appellant has corrected SEQ ID NOS: 7 and 8 in the instant application, this evidence does show that predictability of a correct sequence was not necessarily readily apparent.

The claimed hybridization conditions to a referenced nucleic acid does not result in MAGE TRAP proteins that have all of the identifiable properties or *TRAP characteristics* of MAGE-1 or a MAGE TRAP protein.

The teachings in the specification provide for a plan or an invitation to the skilled artisan to experiment practicing the claimed but do not provide sufficient guidance and specificity how to apply detailed, relevant identifying characteristics in making and using MAGE TRAP proteins that satisfy the TRAP characteristics in order to execute that plan.

In support of the unpredictability of the claimed genus of MAGE TRAP proteins, the evidence supports the contention that strategies drawn to isolating and determining a MAGE TRAP protein that satisfies the TRAP characteristics have not universally straightforward or as easy to apply as was initially hope or disclosed in the specification as-filed nor has the interpretation of results always been unambiguous.

While appellant relies upon hybridizing nucleic acids as the key common structural feature, appellant does not account for the distinguishing structural, expression and functional characteristics of each of the 11 MAGE TRAP species, not all of which meet the critical *characteristics of MAGE TRAPs* asserted in the Brief.

***(ii) MAGE TRAPs are characteristic of cancer cells, and are not expressed by normal cells (with the exception of testis cells).***

Appellant's arguments that the Examples provide 11 species that satisfy the claim limitations have been fully considered but have not been found convincing.

In contrast to appellant's assertions that the disclosed Examples provide 11 species that satisfy the claim limitations, the following is noted.

It is acknowledged that none of the MAGE genes were expressed in a large panel of healthy tissues, with the exception of testis and placenta. (see Abstract and Expression of MAGE genes on pages 366-367 of **De Plaen et al.**).

However, the instant specification does not provide for the expression of each of the disclosed MAGE 1-11 TRAP proteins on cancer cells.

For example, the instant specification does not appear to provide for the expression of MAGE 5-11 nucleic acids in or proteins on normal and cancer cells.

Upon further investigation by the co-inventors, six genes of the MAGE family (MAGE-1, -2, -3, -4, -6 and -12) have been found to be expressed in a number of tumors of various histological types (see Abstract and Expression of MAGE genes on pages 366-367 of **De Plaen et al**.).

Again, Note MAGE-12, which cited by De Plaen et al., was not disclosed in the specification as-filed

MAGE-5, -8, -9, -10 and -11 were very weakly expressed in all samples that have been examined (see page 367, column 1, paragraph 2 of **De Plaen et al**.). .

Again, the disclosed MAGE-7 has not been found to be transcribed and its largest open reading frame was not in phase with those of other MAGE genes (see page 365, column 1, paragraph 1 of **De Plaen et al**).

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 and nucleic acids that hybridize to SEQ ID NO: 8 and any or all of the MAGE TRAP protein properties outlined above.

There is insufficient objective evidence to establish the nexus between SEQ ID NO: 8 and nucleic acids that hybridize to SEQ ID NO: 8 and MAGE TRAP protein expression on a cancer cell obtainable from a melanoma.

***(iv) MAGE TRAPS are processed, intracellularly, into TRAs (tumor rejection antigens), i.e., peptides, which complex to MHC molecules to form targets for cytotoxic T lympyhocytes (CTLs).***

Appellant's arguments that the Examples provide 11 species that satisfy the claim limitations have been fully considered but have not been found convincing.

In contrast to appellant's assertions that the disclosed Examples provide 11 species that satisfy the claim limitations, the following is noted.

Given the conservation of sequences in MAGE genes, it has been suggested that the proteins produced by all of these genes may exert very similar functions. At the time the invention was made and post-filing, there was no indication regarding this function (page 367, column 2, paragraph 3 of **De Plaen et al.).**

It is likely that various regions of the different MAGE proteins can contribute peptides combining with various HLA class I molecules (page 368, column 1, paragraph 2 of **De Plaen et al.**).

This is consistent with the specification as-filed which describes on page 55, paragraph 1 of the specification, which makes clear that the sequences code for **tumor rejection antigen precursors (TRAPS** which, in turn are processed into **tumor rejection antigens (TRAs)**. The evidence points to presentation of TRAs on tumor cells, followed by the development of an immune response and deletion of the cells. TRAPS which are processed into TRAs and the TRAs themselves may be used either alone or in pharmaceutically appropriate compositions as vaccines.

Therefore, the function of a MAGE TRAP protein rests on its ability to be processed, intracellularly, into TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs.

The function of a MAGE TRAP protein to contribute peptides combining with various HLA class I molecules or as a source of a vaccine needed to be tested empirically as the skilled artisan would not have relied solely upon the determination that nucleic acids that hybridize with SEQ ID NO: 8 have been identified, the determination that a MAGE TRAP protein itself may or may not be isolated or the determination that a MAGE TRAP protein may or may not be expressed on a cancer cell.

Even the known MAGE molecules exhibit extremely low immunogenicity and initiation of a strong immune response to tumor antigens is vivo is an extremely rare event (see page 674, paragraph 2 of Kirkin et al., APMIS 106: 665-679, 1998).

Therefore, the reliance upon the function of the claimed tumor rejection antigen precursors depends, in part, upon the antigen processing and presentation of MAGE-derived peptides, which, in turn, can form targets for cytotoxic T cells directed against these peptides.

While such efforts may provide the groundwork for determining a MAGE tumor antigen precursor, "it is difficult to predict whether therapeutic success will be achieve, even if a significant increase in anti-tumor cytotoxic lymphocytes is obtained by immunization" (see Boon et al. (Int. J. Cancer 54: 177-180, 1993; see page 178, column 2, paragraph 2).

Further, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

The specification as-filed does not provide for the tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs), other than SEQ ID NO: 26 for MAGE-1.

The instant specification does not appear to provide for the ability of MAGE 4-11 transfectants to stimulate cytotoxic T lymphocytes.

The instant specification does not appear to provide for the cytotoxic T lymphocytes (CTLs) to test the properties of MAGE 4-11 as MAGE TRAP proteins.

Even with respect to MAGE-2 and –3, it is not readily apparent that the specification as filed provides tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs or for the cytotoxic T lymphocytes (CTLs) to test the properties of MAGE-2 and –3 as MAGE TRAP proteins.

Although appellant has argued and distinguished between different classes of tumor or tumor-associated antigens (e.g. tum- and TSTA) in defining the MAGE family encompassed by the claimed invention, the reliance on the teachings of Stevenson and Boon, in part, was to show that defining or enabling human tumor antigens, including human tumor antigens, that result in stimulating cytotoxic T lymphocytes to tumors was difficult at the time the invention was made.

Although appellant asserts that the degree of immunogenicity is a not a feature of the claims and therefore irrelevant, appellant is reminded of element *(iv) MAGE TRAPS are processed, intracellularly, into TRAs (tumor rejection antigens), i.e., peptides, which complex to MHC molecules to form targets for CTLS* relied upon by appellant in characterizing MAGE TRAP proteins.

Appellant provision in the Brief of a partial Listing of the literature on MAGE TRAPs showing that the molecules are, in fact, immunogenic is acknowledged.

As pointed out above, the specification as filed does not provide for the tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs), other than the specific peptide SEQ ID NO: 26 (EADPTGHSY) which forms a complex with HLA-A1 and stimulates proliferation of CTLs and which is specific for MAGE-1.

In addition to the lack of disclosure for the immunogenic peptides provided with the Listing of TRAPS in the Brief in the specification as-filed, the specification as-filed did not provide written description for the various HLA molecules referenced in this listing. Again, the specification as-filed only provided written support for the specific peptide SEQ ID NO: 26 (EADPTGHSY), which forms a complex with HLA-A1.

The specification as-filed does not provide for the cDNA nor the amino acid sequences as well as isolation for each of the MAGE 1-11 disclosed in the specification as filed.

Given the absence of providing sufficient information (e.g. cDNA or amino acid sequence) concerning MAGE TRAP proteins, the specification as-filed did not provide a sufficient correlation between a particular MAGE TRAP protein and its associated tumor rejection antigens (TRAs) which complex to different MHC molecules to form targets for CTLs.

As indicated above, the specification as-filed did not provide for the cytotoxic T lymphocytes **(CTLs)** to test the properties of each of MAGE 1-11.

The teachings in the specification provide for a plan or an invitation to the skilled artisan to experiment practicing the claimed but do not provide sufficient guidance and specificity how to apply detailed, relevant identifying characteristics in making and using MAGE TRAP proteins that satisfy the TRAP characteristics in order to execute that plan.

In support of the unpredictability of the claimed genus of MAGE TRAP proteins, the evidence supports the contention that strategies drawn to isolating and determining a MAGE TRAP protein that satisfies the TRAP characteristics have not universally straightforward or as easy to apply as was initially hope or disclosed in the specification as-filed nor has the interpretation of results always been unambiguous.

While appellant relies upon hybridizing nucleic acids as the key common structural feature, appellant does not account for the distinguishing structural, expression and functional characteristics of each of the 11 MAGE TRAP species, not all of which meet the critical *characteristics of MAGE TRAPs* asserted in the Brief.

With respect to the reliance of the claimed MAGE tumor rejection antigen precursors proteins on antigen processing and presentation and recognition by cytototoxic T cells directed against peptides derived from said MAGE proteins, it is acknowledged that cytotoxic T cells can be used in vitro rather than in vivo in response to appellant's comments.

**B) Appellant Asserts That The Rejection of Claims 184, 187 and 190 for Failing to Satisfy the Enablement Requirement of 35 USC 112, first paragraph is Erroneous and Should be Reversed**

Appellant notes that each of claims 184, 187 and 190 required that the MAGE tumor rejection antigen precursor includes the nine amino acid sequence of SEQ ID NO: 26, which has been shown to function as a tumor rejection antigen which forms a complex with HLA-A1 molecules an stimulates proliferation of cytotoxic T lymphocytes (CTLs) (see U.S. Patent No. 5,925,729 and Example 34 of the instant specification).

Appellant asserts that the claims require a commonality of structure and that the USPTO has accepted the proposition that SEQ ID NO: 26 is a tumor rejection antigen (TRA).

However, appellant has not provided for a nucleic acid or an amino acid that encodes a MAGE TRAP protein other than MAGE-1 itself that when processed can result in the stimulation of a CTL that recognizes the specific peptide SEQ ID NO: 26.

As indicated, in part, above in Section (A), the specification does not provide for the cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein other than MAGE-1 itself that can provide for the antigen presentation of SEQ ID NO: 26 to CTLs.

The claims are not limited to MAGE-1.

Further, the specification as filed does not even provide for the structure and diversity of MAGE-1.

As pointed out above, the specification as filed does not provide for the tumor rejection antigens (TRAs, i.e. peptides, which complex to MHC molecules to form targets for CTLs), other than the specific peptide SEQ ID NO: 26 (EADPTGHSY) which forms a complex with HLA-A1 and stimulates proliferation of CTLs and which is specific for MAGE-1.

According to the listing of TRAPS submitted with the Brief, it appears that SEQ ID NO: 26 (EADPTGHSY) of MAGE-1 can complex with HLA B35. However, the specification as-filed does not provide a written description for this observation that SEQ IDNO: 26 can complex with HLA molecules other than HLA-A1.

As disclosed on page 30, paragraph 2 of the instant specification, in isolating the pertinent nucleic acid sequence for a tumor rejection antigen precursor, the techniques developed by appellant showed that a recipient cell is needed which fulfills two criteria: (i) the recipient cell must not express the TRAP of interest under normal conditions, and (ii) it must express the relevant class I HLA molecule.

Consistent with the specification as filed and appellant's arguments, it is likely that various regions of the different MAGE proteins can contribute peptides combining with various HLA class I molecules (page 368, column 1, paragraph 2 of **De Plaen et al.**).

Therefore, it was necessary to have the appropriate CTLs readily available and know what was the relevant class I HLA molecule associated with each MAGE TRAP protein in order to determine whether a MAGE TRAP protein satisfied the four criteria *(i) – (iv)* for a MAGE TRAP.

The specification as-filed does not appear to provide for a CTL to test whether MAGE-1 TRAP protein or a MAGE TRAP protein comprising SEQ ID NO: 26 can complex with HLA B35, as relied upon by appellant in providing the listing of TRAP immunogenic peptides.

In addition to the lack of written support for the immunogenic peptides provided with the Brief in the specification as-filed, the specification as-filed did not provide written description for the various HLA molecules referenced in this listing. Again, the specification as-filed only provided written support for the specific peptide SEQ ID NO: 26 (EADPTGHSY) which forms a complex with HLA-A1.

The specification as-filed does not provide for the cDNA nor the amino acid sequences as well as isolation for each of the MAGE 1-11 disclosed in the specification as filed.

Given the absence of providing sufficient information (e.g. cDNA or amino acid sequence) concerning MAGE TRAP proteins, the specification as-filed did not provide a sufficient correlation between a particular MAGE TRAP protein and its associated tumor rejection antigens (TRAs) which complex to different MHC molecules to form targets for CTLs.

As noted above, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

Given that the claims encompass nucleic acids that hybridize to SEQ ID NO: 8 and Given that "variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2 or Kirkin et al.), appellant was not in possession of a genus of MAGE TRAP proteins comprising SEQ ID NO: 26 wherein the MAGE TRAP protein relies upon nucleic acids that hybridize to SEQ ID NO: 8. Given the hybridization language encompassed by the claims, the claimed MAGE TRAP proteins comprise variations in amino acid sequences. Therefore, there is insufficient evidence that appellant was in enabling a genus of MAGE TRAP proteins comprising SEQ ID NO: 26 that would provide SEQ ID NO: 26 itself and, more importantly, provide SEQ ID NO: 26 that is recognized by an appropriate CTL.

The teachings in the specification provide for a plan or an invitation to the skilled artisan to experiment practicing the claimed but do not provide sufficient guidance and specificity how to apply detailed, relevant identifying characteristics in making and using MAGE TRAP proteins that satisfy the TRAP characteristics in order to execute that plan.

In support of the unpredictability of the claimed genus of MAGE-TRAP proteins, the evidence supports the contention that strategies drawn to isolating and determining a MAGE TRAP protein that satisfies the TRAP characteristics have not universally straightforward or as easy to apply as was initially hope or disclosed in the specification as-filed nor has the interpretation of results always been unambiguous.

The teachings in the specification provide for a plan or an invitation to the skilled artisan to experiment practicing the claimed but do not provide sufficient guidance and specificity how to apply detailed, relevant identifying characteristics in making and using MAGE TRAP proteins that satisfy the TRAP characteristics in order to execute that plan.

While appellant relies upon hybridizing nucleic acids as the key common structural feature, appellant does not account for the distinguishing structural, expression and functional characteristics of each of the 11 MAGE TRAP species, not all of which meet the critical *characteristics of MAGE TRAPs* asserted in the Brief.

**C) Examiner Submits That The Rejection of Claims 189-191 for Failing to Satisfy the Enablement Requirement of 35 USC 112, first paragraph Should Stand or Fall Together**

As described on page 55, paragraph 1 of the specification, the disclosure make clear that the sequences code for **tumor rejection antigen precursors (TRAPS** which, in turn are processed into **tumor rejection antigens (TRAs)**. The evidence points to presentation of TRAs on tumor cells, followed by the development of an immune response and deletion of the cells. TRAPS which are processed into TRAs and the TRAs themselves may be used either alone or in pharmaceutically appropriate compositions as vaccines.

The following definition of a vaccine is found on page 309 of the Illustrated Dictionary of Immunology, Cruse and Lewis, CRC Press, Boca Raton, FL, 1994.

Vaccine: Live attenuated or killed organisms or parts or products from them which contain antigens that can stimulate a specific immune response consisting of protective antibodies and T cell immunity. A vaccine should stimulate a sufficient number of memory T and B lymphocytes to yield effector T cells and antibody-producing B cells from memory cells. It should also be able to stimulate high titers of neutralizing antibodies. Invention of a vaccine into a nonimmune subject induces active immunity against the modified pathogens.

As indicated, in part, above in Sections (A) and (B), the specification does not provide for the cDNA or amino acid sequence as well as the isolation of a MAGE tumor rejection antigen precursor protein other than MAGE-1 itself that can provide for the antigen presentation to CTLs and, in turn, serve as a vaccine.

As indicated, in part, above in Sections (A) and (B) with respect to MAGE tumor antigen precursors, "it is difficult to predict whether therapeutic success will be achieve, even if a significant increase in anti-tumor cytotoxic lymphocytes is obtained by immunization" (see Boon et al. (Int. J. Cancer 54: 177-180, 1993; see page 178, column 2, paragraph 2).

Further, Kirkin et al. (APMIS 106: 665-679, 1998) reviews melanoma-associated antigens recognized by cytotoxic T lymphocytes and notes their genuinely low immunogenicity (see entire document, including Abstract on page 665 and Immunogenicity of tumor cells on pages 673-674). For example, "from an immunological point of view, the MAGE antigens represent very good targets for immunotherapy" and yet "so far only one patient has shown an immune response to this group of antigens, suggesting an extremely low immunogenicity of the MAGE antigens" (see page 669, column 2, paragraph 1). The authors further note that "it should nevertheless be taken into account that some variations in amino acid sequence in the epitope flanking region lead to generation of a cleavage portion inside the epitope which may destroy the antigenic site" (see page 674, column 2).

The claims are not limited to those MAGE TRAP proteins that have been shown to be sufficiently immunogenic to serve as a vaccine.

Further, the specification as filed does not provide for the structure and diversity of MAGE TRAPs and their ability to serve as a vaccine.

As indicated above, not each one of MAGE 1-11 disclosed in the specification as filed is expressed on a cancer cell.

Nucleic acids of which the complementary sequences hybridize to SEQ ID NO: 8 do not provide sufficient written description provision of 35 USC 112, first paragraph for a genus of diverse tumor rejection antigen precursors, including the four characteristics for MAGE TRAPS, particularly the ability of the genus of MAGE TRAPS to serve as a vaccine.

The instant specification does not appear to provide for a genus of MAGE tumor rejection antigen precursor proteins that are expressed on cancer cells and, in turn, can serve as a vaccine, such as providing tumor rejection antigens (TRAs) for the antigen presentation to CTLs.

As disclosed on page 30, paragraph 2 of the instant specification, in isolating the pertinent nucleic acid sequence for a tumor rejection antigen precursor, the techniques developed by appellant showed that a recipient cell is needed which fulfills two criteria: (i) the recipient cell must not express the TRAP of interest under normal conditions, and (ii) it must express the relevant class I HLA molecule.

Therefore, it was necessary to have the appropriate CTLs readily available and know what was the relevant class I HLA molecule associated with each MAGE TRAP protein in order to determine whether a MAGE TRAP protein satisfied the four criteria *(i) – (iv)* for a MAGE TRAP.

The specification as-filed does not appear to provide for a CTL to test whether MAGE-1 TRAP protein or a MAGE TRAP protein comprising SEQ ID NO: 26 can complex with HLA B35, as relied upon by appellant in providing the listing of TRAP immunogenic peptides.

In addition to the lack of written support for the immunogenic peptides provided with the Brief in the specification as-filed, the specification as-filed did not provide written description for the various HLA molecules referenced in this listing. Again, the specification as-filed only provided written support for the specific peptide SEQ ID NO: 26 (EADPTGHSY) which forms a complex with HLA-A1.

The specification as-filed does not provide for the cDNA nor the amino acid sequences as well as isolation for each of the MAGE 1-11 disclosed in the specification as filed.

Given the absence of providing sufficient information (e.g. cDNA or amino acid sequence) concerning MAGE TRAP proteins, the specification as-filed did not provide a sufficient correlation between a particular MAGE TRAP protein and its associated tumor rejection antigens (TRAs) which complex to different MHC molecules to form targets for CTLs.

In support of the unpredictability of the claimed genus of MAGE TRAP proteins, the evidence supports the contention that strategies drawn to isolating and determining a MAGE TRAP protein that satisfies the TRAP characteristics have not universally straightforward or as easy to apply as was initially hope or disclosed in the specification as-filed nor has the interpretation of results always been unambiguous

The teachings in the specification provide for a plan or an invitation to the skilled artisan to experiment practicing the claimed but do not provide sufficient guidance and specificity how to apply detailed, relevant identifying characteristics in making and using MAGE TRAP proteins that satisfy the TRAP characteristics in order to execute that plan.

In support of the unpredictability of the claimed genus of MAGE TRAP proteins, the evidence supports the contention that strategies drawn to isolating and determining a MAGE TRAP protein that satisfies the TRAP characteristics have not universally straightforward or as easy to apply as was initially hope or disclosed in the specification as-filed nor has the interpretation of results always been unambiguous.

While appellant relies upon hybridizing nucleic acids as the key common structural feature, appellant does not account for the distinguishing structural, expression and functional characteristics of each of the 11 MAGE TRAP species, not all of which meet the critical *characteristics of MAGE TRAPs* asserted in the Brief.

**(12)** For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

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Conferee